REMARKS

A. State of Claims

Claims 2-4, 6-35, 37-41 and 52-61 are currently pending. Claim 56-61 have been withdrawn by the Examiner. Claims 7, 11, 16, 24, 52, 53, and 55 have been amended in the Amendment set forth herein. Claim 54 has been canceled. Claims 2-4, 6-35, 37-41 and 52-53, and 54-55 are under examination.

B. Withdrawal of Claims 56-61

The Examiner has withdrawn claims 56-61, which are generic in scope as to the targeting ligand, on the basis of 37 C.F.R. §1.142(b) and MPEP §821.03, taking the position that the new claims are directed to "independent or distinct" subject matter.

Applicants respectfully traverse and request reconsideration prior to petitioning. It is noted that rather than being independent and distinct, claims 56 and 58 are generic in scope and are identical to pending claims 33 and 35, except they recite simply a "tissue specific ligand" rather than the sub-generic species recited in claims 33 and 35. Furthermore, it should be noted that new claims 56 and 58 are essentially identical to claims 33 and 35 as originally presented, and found by this same Examiner to be directed to the same invention as the claims currently under examination. See Restriction Requirement dated September 27, 2001. In that restriction requirement, the present Examiner found that Group II comprised claims 33-41, and the Applicants in response elected group II. It is reiterated that current claims 56 and 58 are virtually identical to elected claims 33 and 35.

Lastly, it is noted that withdrawn claims 59 and 60-61 are virtually identical in scope to the pending claims. Thus, the Examiner is requested to explain on this record how these claims are considered to be independent and distinct from the current claims.

Thus, it is submitted to be improper for the Examiner to withdraw claims 56-61 from active prosecution.

C. 14-Page Information Disclosure Statement

The Examiner has commented upon Applicants' recent 14-page information disclosure statement [sic, form 1449] having approximately 185 references.

First of all, Applicants apologize for the additional burden imposed by the references, but the undersigned felt that submission of these references was arguably required. Applicants would, however, like to take this opportunity to explain the reason for this extensive reference citation at this stage of the prosecution. First, a few of the references were identified as of record in related cases USSN 10/703,405, 10/732,919 and U.S. Patent 6,692,724 that were inadvertently not previously made of record in the present case. So, these references were submitted out of an abundance of caution and to ensure that all related cases have a consistent set of references of record.

Most of the 185 newly submitted references come from unrelated cases, USSN 10/126,216, 10/126,369 and 10/327,455. These cases are directed to similar subject matter as the present case and are assigned to the same assignee but have a different inventive entity. They were not earlier submitted since the cases are being handled by another law firm, were previously unknown to the undersigned and have just recently been brought to the undersigned attention.

The present Examiner should also consider the pending claims in the related cases to ensure that no double patenting rejection is appropriate.

Finally, the Examiner states that it is the Applicants' "obligation to call the most pertinent prior art" to the Examiner's attention. Applicants would appreciate the Examiner pointing out precisely what rule is being referred to – we understand that such a rule was

previously in place prior to 1994 but do not believe that the current rules make this requirement. If we are incorrect in this regard, please let us know and we will be happy to comply with this request.

In the response to the enablement rejections under 35 U.S.C. 112, first paragraph, and the indefiniteness rejections under 35 U.S.C. §112, second paragraph, Applicants, as set forth below, have included the Declaration of Jerry L. Bryant, M.S. This Declaration includes 64 references that are cited as Exhibits. Applicants have herein included a form 1449 that lists those references set forth in the Declaration that have not been previously made of record. Applicants apologize for any additional burden imposed by these references.

D. Amendments to the Specification

In the specification, page 14, line 10 of the specification has been amended to correct a typographical error in the legend for FIG. 39. In particular, FIG. 39 has no subparts A and B. The figure legend has been amended to delete reference to subparts A and B.

E. Objections to the Claims

Claims 7, 11-14, 16-22, 24-29, and 52-55 are objected to as being dependent upon a rejected base claim. The Examiner indicates that these claims would be allowable if rewritten in independent form, including all of the limitations of the base claim and any intervening claims. Applicants, in the Amendment to the claims set forth herein, have amended claims 7, 11, 16, 24, 52, 53, and 55 in accordance with the Examiner's suggestion. Claim 54 has been canceled because it is a substantial duplicate of claim 53. Therefore, the objections have been overcome.

F. Rejection based on 35 U.S.C. 112, first paragraph

The Action rejects claims 2-4, 6, 8, 10, 15, 23, 30, 31, 33-35, and 37-41 under 35 U.S.C. §112, first paragraph, as not being enabled for the full scope of the claimed invention, in particular, methods of synthesizing EC conjugates of anticancer agents, tumor markers, folate

receptor targeting ligands, tumor apoptotic cell targeting ligands, tumor hypoxia targeting ligands, or agents that mimic glucose. Applicants respectfully traverse.

35 U.S.C. §112, first paragraph, states in part that "[t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same." 35 U.S.C. §112, first paragraph. It is permissible for some experimentation to be required to practice the claimed invention, so long as it is not undue. *Atlas Powder Co. v. E.I. Dupont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984). Applicants also note that "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claims, then the enablement requirement is satisfied." *MPEP* §2164.01(b) citing *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

1. U.S. Patent 6,692,724

The present Applicants were somewhat surprised to find that this rejection has been maintained in the present case. In Applicants companion case being examined by the same Examiner, USSN 09/434,313, the same language rejected in the present case has been found acceptable based on essentially the same specification. Indeed, the '313 application has recently issued as U.S. Patent 6,692,724, copy enclosed, and was allowed and issued subsequent to the entry of the rejections in the present case. This issued patent is, of course, presumed valid and the claim language presumed to be enabled and fully described in the specification. As such, the '724 patent is strong evidence that the claims here satisfy both requirements. Applicants believed that upon reconsideration of the evidence presented herein that the Examiner will agree that the rejections are improper.

2. No factual basis is provided to support rejection of claims 2-4, 6, 8, 10, 15, 23, 30, 31, 33-35, and 37-41 under 35 U.S.C. §112, first paragraph

First, Applicants observe that the Action again provides no factual basis to rebut the teachings of the specification or support the premise that one skilled in the art would have to undertake undue experimentation to "obtain a tissue specific ligand, wherein the tissue specific ligand is an anti-cancer agent, a tumor marker, a folate receptor targeting ligand, a tumor apoptotic cell targeting ligand, a tumor hypoxia targeting ligand, or an agent that mimics glucose...admixing said ligand with ethylenediceysteine (EC) to obtain an EC-tissue specific ligand derivative; and...admixing said EC-tissue specific ligand derivative with a radionuclide and a reducing agent to obtain a radionuclide labeled EC-tissue specific ligand derivative, wherein the EC forms an N_2S_2 chelate with the radionuclide." The Examiner is referred specifically to *MPEP* §2164.04, which provides that it is the Examiner's burden to come forward with factual evidence that would raise a "doubt as to the objective truth of the statements" contained in the application regarding enablement. See, *e.g.*, *In re Marzocchi*, 169 U.S.P.Q. 367, 370 (CCPA 1971). This has not been done here.

Contrary to the Examiner, Applicants presented substantial factual support in their last response, in accordance with the factors of *In re Wands*, to which the Examiner has not responded. Applicants provide once again herein the previous factual presentation along with a more detailed analysis of the support that includes the Declaration of Jerry L. Bryant, M.S., which, as discussed below, provides a detailed demonstration of the enablement of the claims.

3. Undue experimentation is not needed to practice the invention of claims 2-4, 6, 8, 10, 15, 23, 30, 31, 33-35, and 37-41

In light of the teachings of the specification and the level of skill in the art, undue experimentation is *not needed* for one of ordinary skill in the art to synthesize a tissue specific ligand-EC conjugate (EC-ligand conjugate) as claimed. Factors to be considered include (1) the nature of the invention, (2) state of the prior art (3) level of one of ordinary skill in the art, (4)

level of unpredictability in the art, (5) amount of direction an guidance provided by the inventor (6) existence of working examples (7) breadth of the claims and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

a. The art related to the claimed invention was well developed and skill in the art was high

As stated in the Action on page 4, the nature of the invention is directed to methods of synthesizing EC-tissue specific ligand complexes. The state of the art is one in which radiolabeling of N_2S_2 chelates was known, as exemplified by the Anderson *et al.* 1995, citation on page 5 of the Action. Also known in the art were synthetic methods for conjugating imaging agents to targeting agents based on the available functional groups of the targeting agent, *see* U.S. Patent 5,517,993 column 7, line 53 to column 8, line 26. Thus, one of ordinary skill in the art of imaging agent conjugation possessed a high level of skill in conjugating imaging agents to targeting agents. The Examiner is also directed to the Declaration of Jerry L. Bryant, discussed in greater detail below, which provides additional evidence that the state of the art pertaining to conjugation of imaging agents to targeting agents was well-developed.

b. The specification provides sufficient guidance to one of skill in the art for the purpose of selecting a targeting agent

One of ordinary skill in the art, in light of the specification, could have readily selected a targeting agent to be used in the claimed methods for synthesizing an EC-tissue specific ligand conjugate. Applicants provide guidance to the skilled artisan by means of a number of examples illustrating the coupling of EC to a representative number of tissue specific ligands. The tissue specific ligands described in the specification are representative of the various classes of tissue specific agents, including anti-cancer agents (specification, page 5, line 16-18), tumor markers (specification, page 5, line 18-21), folate receptor targeting ligands (specification, page 5 line

23), tumor apoptotic and tumor hypoxia cell targeting ligands (specification, page 5, line 24-25), and agents that mimic glucose (specification, page 5, Line 29 to page 6, line 2).

In further support, Applicants reference the scientific literature to demonstrate that one of skill in the art, based on the teachings of the specification, would be able to readily identify and select a tissue specific ligand of the invention. There are a variety of methods known in the art for the identification of ligands and the characterization of the identified ligand as an anticancer agent (Yamori *et al.*, 1999 – *in vitro* and *in vivo* growth inhibition assays), a tumor marker (Hibi *et al.*, 1999; Becker *et al.*, 1999 – northern blotting western blotting and immunohistochemisttry), a folate receptor targeting ligand (Sudimack and Lee, 2000 – radiolabeled ligand binding), a tumor apoptotic cell targeting ligand (Takamizawa *et al.*, 2000 – RNase protection and western blotting assays), a tumor hypoxia targeting ligand (Garayoa *et al.*, 2000 – northern blotting, immunohistochemistry, and luciferase reporter assays), or an agent that mimics glucose (Kanazawa *et al.*, 1997 – *in vivo* distribution studies and NMR analysis). Specifically, the specification identifies various anticancer agents in Table 2 on pages 34-41. In addition, Yamori *et al.*, on page 4043, describe methods that exemplify the identification of anticancer agents by analysis of cell growth inhibition and antitumor activity against nude mouse xenografts. Hibi *et al.* describe using northern blot, western blot, and immunohistochemical analysis of various cancer cells and non-cancer cells to identify the tumor marker PGP9.5. Becker *et al.* describe the use of a monoclonal antibody as a tumor marker to identify tumor cells expressing an aberrant form of E-cadherin.

Detection of folate receptor targeting is exemplified in Sudimack and Lee (2000) on page 151 to 152 where localization of a folate receptor ligand is accomplished by *in vitro* and *in vivo* radiolabeled ligand studies. An example of tumor apoptotic cell targeting ligand identification is provided in Takamizawa *et al.* where the expression of proapoptotic proteins is assayed by RNase protection and western blotting assays. A tumor hypoxia targeting ligand may be

identified by using northern blotting, immunohistochemistry, and luciferase reporter assays in conjunction with hypoxic cell culture as described in Garayoa *et al.*. Kanazawa *et al.* identify the tumor localization of glucose mimics or analogs by using *in vivo* distribution studies and NMR analysis. Any of these methods in combination with the guidance provided may be used for identifying a tissue specific agent of the invention. The Declaration of Jerry L. Bryant, M.S., discussed in greater detail below, provides additional evidence that the specification provides sufficient guidance to one of skill in the art for the purpose of selecting a targeting agent.

c. The specification provides sufficient guidance to one of skill in the art for purposes of identifying the necessary conjugation chemistry

If the Examiner's concerns are related to the presence of appropriate functional groups on the selected tissue specific ligand, the specification provides a detailed description of the conjugation chemistry. Applicants refer the Examiner to at least page 6, lines 4-18; page 22, line 18 to page 23, line 23; FIG. 1-3, 7, 8A, 16, 21, 36, 49, 54, and 59 for a detailed description of the chemistry and functional groups underlying the conjugation of EC to representative tissue specific ligands. Of particular interest is Table 1 on page 23 of the specification that illustrates exemplary linkers that can be used to conjugate EC to a variety of functional groups. One of skill in the art is capable of identifying a functional group(s) of a tissue specific ligand that is useful for the synthetic methods claimed.

The Declaration of Jerry L. Bryant, M.S., discussed in greater detail below, provides additional evidence that the specification provides sufficient guidance to one of skill in the art for the purpose of identifying the necessary conjugation chemistry.

d. Routine imaging and distribution studies

Once an EC-conjugate is synthesized according to the present invention, one of skill can readily confirm its imaging capabilities through the application of imaging studies such as the cellular uptake and distribution studies exemplified throughout the examples section, pages 32-

68 of the specification. In particular, cellular uptake studies are exemplified throughout the examples section and in FIGs. 46-48, 55-58, 69-73, and 76-80; whereas distribution studies are exemplified throughout the examples section and in FIGs. 6, 11, 12, 14, 15, 17-20, 25, 26, 28-35, 37, 81-86. No undue experimentation is needed to carry out the teachings of the specification and perform the claimed methods for synthesizing imaging conjugates.

Claims may be rejected if persons skilled in the art must resort to elaborate, considerable, or unreasonable experimentation in order to practice an invention. In light of the foregoing, such undue experimentation is *not required* to practice the methods for synthesizing an EC-tissue specific ligand conjugate. The Declaration of Jerry L. Bryant, M.S., discussed in greater detail below, provides additional evidence that undue experimentation is not required to practice the methods for synthesizing EC-tissue specific ligand conjugates of the claimed invention.

4. Declaration of Jerry L. Bryant, M.S.

As set forth above, the Examiner has failed to meet his burden of coming forward with factual evidence that would raise a "doubt as to the objective truth of the statements" contained in the application regarding enablement. See, *e.g.*, *In re Marzocchi*, 169 U.S.P.Q. 367, 370 (CCPA 1971). As set forth above, Applicants have provided ample evidence of enablement.

Applicants provide herein even further evidence of enablement by submitting, as Exhibit A, the Declaration of Jerry L. Bryant, M.S. It should be noted that in accordance with *MPEP* §2164.05, "Applicants may submit factual affidavits or cite references to show what one skilled in the art knew at the time of filing the application." *MPEP* §2164.05. "A Declaration or affidavit is, itself, evidence that must be considered." *MPEP* §2164.05 (emphasis added).

Mr. Bryant has expertise in the synthesis and use of radionuclide imaging agents. His expertise includes employment as Chief Technology Officer of several business entities that are involved with research directed to the synthesis and use of radionuclide imaging agents, a co-inventorship on three patent applications pertaining to novel radionuclide imaging agents and

imaging technologies, involvement in funded studies pertaining to the development of radionuclide imaging agents and their use in imaging, and authorship of numerous reference materials pertaining to the synthesis of radionuclides and their use as imaging agents. See paragraphs 1-3 of Exhibit A. Mr. Bryant has reviewed the present patent application and the Office Actions dated September 29, 2003 and June 25, 2004, and he has an understanding of the rejections that have been set forth by the Examiner. See paragraphs 4-6 of Exhibit A.

As a scientist who has expertise in the synthesis and use of radionuclides, Mr. Bryant sets forth in his Declaration his belief that the invention set forth in the present application provides for novel diagnostic and therapeutic radiopharmaceuticals that can be broadly applied by scientists and clinicians, and that the chemistry of the technology is such that those of ordinary skill in the synthesis of radiolabeled imaging agents will be able to make and use the claimed radiolabeled imaging agents without an undue amount of experimentation. See paragraphs 7 and 8 of Exhibit A. Furthermore, Mr. Bryant has declared that "[w]ithout reservation, I believe that if a skilled expert had the foresight to invent and develop this technology many years ago, it would be in routine use by scientists in the laboratory and clinicians in the hospital." Paragraph 9 of Exhibit A.

Mr. Bryant has declared that one skilled in the imaging and use of radionuclide imaging agents would have been enabled to make and use the claimed invention when presented with the information provided in the specification, and the specification, with its numerous working examples, provides sufficient guidance to predictably identify the targeting ligands and EC-targeting ligand complexes without an undue amount of experimentation. See paragraphs 10-11 of Exhibit A. In support of his statements pertaining to enablement, he sets forth summaries of information pertaining to support provided in the specification and reference materials available at around the priority date of the instant invention that would support enablement. This information, that is detailed in his Declaration, is summarized as follows.

a. Claims Pertaining to Anticancer Agents

Mr. Bryant has declared that the entire specification provides a substantial amount of information regarding embodiments of the claimed invention wherein the tissue specific ligand is an anticancer agent, the conjugation chemistry of anticancer agents as targeting ligands, and information pertaining to the preparation of EC-anticancer agent derivatives. See paragraphs 12-14 of Exhibit A. For example, he indicates that exemplary anticancer agents are set forth in Table 2 of the specification. See paragraph 12, Exhibit A. Exemplary radiolabeled ligands wherein the targeting ligand is an anticancer agent are also set forth in the specification, such as on page 6, line 30 through page 7, line 4, and Table 1, page 23. See paragraph 14 of Exhibit A.

Furthermore, Mr. Bryant declares that around the time of the priority date, numerous anticancer agents were known and widely used in the treatment of cancer, and that the phrase "anticancer agent" would have been readily understood to refer to agents such as chemotherapeutic drugs that had been widely used by scientists and clinicians for many years. See paragraph 15 of Exhibit A. Furthermore, the use of anticancer agents as targeting ligands was well-known at around the time the application was filed in the context of unrelated inventions, and he has identified numerous examples wherein anticancer agents were known to be used as targeting ligands. See paragraph 16 of Exhibit A. Furthermore, Mr. Bryant describes the state-of-the-art around the time of filing pertaining to use of anticancer agents as targeting ligands in conjugates for imaging. See paragraph 17, Exhibit A. For example, he has cited publications of the present inventors, including Zareneyrizi *et al.*, 1999 (Exhibit 18 of Exhibit A), which describes the use of ^{99m}Tc-EC-colchicine for imaging studies, and Yang *et al.*, 1999a (Exhibit 19 of Exhibit A) which describes the synthesis of ^{111}In-labeled DTPA-methotrexate for use in imaging. See paragraph 17 of Exhibit A. Thus, the state-of-the-art pertaining to anticancer agents and their use as targeting ligands was well-developed in the context of unrelated inventions.

In view of the above, Mr. Bryant has concluded that one skilled in the synthesis and use of radiolabeled imaging agents would have understood, from reading the specification, that an "anticancer agent" is a phrase used to refer to a member of a specific group of agents that can readily identified by *in vitro* and/or *in vivo* studies, that anticancer agents can be used as targeting ligands, and that the science related to this area was highly developed at around the priority date. See paragraph 18, Exhibit A. As a result, he declares that "one of ordinary skill in the synthesis and use of radionuclide imaging agents, upon reading the specification of the present application, would have been able to make and use the claimed radionuclide-labeled anticancer agents without an undue amount of experimentation." Paragraph 18, Exhibit A.

b. Claims Pertaining to Tumor Markers

Mr. Bryant has identified a substantial amount of information in the specification pertaining to claims that include a tumor marker as the tissue-specific ligand. See paragraph 19 of Exhibit A. Exemplary sections include page 5, lines 5-14 and page 5, line 22. See paragraph 19 of Exhibit A. Furthermore, he has indicated that the specification provides substantial guidance regarding the synthesis of EC-tumor marker derivatives. See paragraph 20 of Exhibit A. For example, information regarding conjugation chemistry of ligands such as tumor markers can be found on page 22, line 18 through page 23, line 21. See paragraph 20 of Exhibit A. Furthermore, Mr. Bryant has indicated that around the time of the priority date of the referenced patent application, the state-of-the-art pertaining to tumor markers and their use as targeting ligands was well-established. See paragraph 21 of Exhibit A. Numerous examples of tumor markers are set forth in paragraph 21 of Exhibit A, and numerous examples of tumor markers used as targeting ligands are set forth in paragraph 22 of Exhibit A. Furthermore, he was aware of a publication of the inventors that described an imaging agent that included a tumor marker as a targeting ligand. See paragraph 22 of Exhibit A, citing Kim *et al.*, 2000 (Exhibit 30 of Exhibit A). Thus, in view of the information known to those of ordinary skill in the art, Mr. Bryant

declares that "one of ordinary skill in the synthesis and use of radiolabeled imaging conjugates, upon reading the specification, would have been able to make and use the claimed radiolabeled conjugates without an undue amount of experimentation." Paragraph 22 of Exhibit A. Furthermore, one skilled in the synthesis and use of radionuclide imaging agents would have understood that a tumor marker refers to a member of a group of agents that can be readily identified by techniques commonly used by those of ordinary skill in the art. See paragraph 23 of Exhibit A.

c. Claims Pertaining to Folate Receptor Targeting Ligands

Mr. Bryant has identified detailed information in the specification pertaining to folate receptor targeting ligands and the preparation of radiolabeled folate receptor targeting ligands. See paragraph 24 of Exhibit A. Exemplary folate receptor targeting ligands are set forth on page 5, line 23 and page 6, lines 4-19. See paragraph 24 of Exhibit A. Mr. Bryant has also found that the specification provides substantial guidance pertaining to the preparation of EC-targeting ligand derivatives, including, for example, page 7, lines 5-13 and page 20, lines 7-15. See paragraph 25 of Exhibit A. Furthermore, he has declared that around the priority date of the present patent application, there was a substantial amount of information pertaining to folate receptors and folate receptor targeting ligands that was known in the art in the context of unrelated inventions. See paragraph 26 of Exhibit A. In addition, folate analogs were used in various contexts as targeting ligands, and numerous such examples are disclosed in paragraph 27 of Exhibit A. Regarding the development and use of radiolabeled agents for imaging, Mr. Bryant was aware that ^{99m}Tc-EC-folate had been described as a new tumor imaging agent in a publication of the inventors. See paragraph 28 of Exhibit A, citing Ilgan *et al.*, 1998 (Exhibit 40 of Exhibit A).

In view of the information known in the art at the time of the priority date of the instant invention, Mr. Bryant has declared that one of ordinary skill in the art would have been able to

make and use the claimed radionuclide-labeled folate receptor targeting ligand conjugates without an undue amount of experimentation, and that the skill in the art as to folate receptor targeting was very high at the time of the priority date. See paragraphs 28 and 29 of Exhibit A. Furthermore, he notes that one of ordinary skill in the synthesis and use of radionuclide imaging agents would have understood that a "folate receptor targeting agent" refers to a member of a group of agents that can be readily identified using techniques well-known to those of ordinary skill in the art. See paragraph 29 of Exhibit A.

d. Claims Pertaining to Tumor Apoptotic Cell Targeting Ligands

Mr. Bryant has reviewed the specification, and has found that it provides substantial guidance regarding aspects of the invention that pertain to radiolabeled conjugates wherein the targeting ligand is a tumor apoptotic cell targeting ligand. See Paragraph 30 of Exhibit A. This support includes exemplary tumor apoptotic targeting ligands, information pertaining to the conjugation chemistry of tumor apoptotic targeting ligands, information pertaining to the imaging of tumor apoptotic cells, and a working example pertaining to a radiolabeled conjugate that includes annexin-V, and guidance pertaining to the preparation of EC-targeting ligand conjugates and radiolabeling of EC-targeting ligand derivatives. See paragraphs 30 and 31 of Exhibit A.

In addition, Mr. Bryant has indicated that around the time of the priority date of the present application, it was well-established that apoptosis plays a critical role in the pathophysiology of cancer, and that markers of apoptosis had been identified and were the subject of active investigation in the context of unrelated inventions. See paragraphs 32 and 33 of Exhibit A. Tumor apoptotic cell targeting ligands, exemplified by annexin V, would have been known to refer to a very limited number of specific compounds which are capable of detecting the death of tumor cells. See paragraph 34 of Exhibit A. The state-of-the-art related to apoptotic cell targeting ligands was well-established. See paragraph 34 of Exhibit A.

Therefore, in view of the above, Dr. Bryant declares that "one of ordinary skill in the synthesis and use of radionuclide imaging agents, upon reading the specification, would have been able to make and use the claimed radionuclide-labeled apoptotic cell targeting ligand conjugates without an undue amount of experimentation." Paragraph 35 of Exhibit A. Furthermore, "one of ordinary skill in the synthesis and use of radionuclide imaging agents would have understood that an 'apoptotic cell targeting ligand' refers to a member of a specific group of agents that can be readily identified" using techniques well-known to those of ordinary skill in the art. Paragraph 35 of Exhibit A.

e. Claims Pertaining to Tumor Hypoxia Targeting Ligands

Upon review of the specification, Mr. Bryant has found that there is substantial support in the specification for methods of the invention that involve tumor hypoxia targeting ligands and conjugates involving tumor hypoxia targeting ligands. See paragraph 36 of Exhibit A. This information includes exemplary tumor hypoxia targeting ligands, information pertaining to the conjugation chemistry of such targeting ligands, and information pertaining to the preparation of EC-tumor hypoxia targeting ligand conjugates, including a working example pertaining to the synthesis and stability of ^{99m}Tc-EC-metronidazole. See paragraph 36 of Exhibit A.

Mr. Bryant has declared that around the time of filing of the present patent application, there was substantial information available regarding tumor hypoxia targeting ligands. See paragraph 38 of Exhibit A. Exemplary tumor hypoxia targeting ligands, including use of one such targeting ligand in imaging, are set forth in paragraph 38 of Exhibit A. Dr. Bryant also indicates that Yang *et al.* (Exhibit 57 of Exhibit A, a publication of the inventors), had developed a ^{99m}Tc-labeled metronidazole using EC as a chelator and determined that it was feasible to use this agent to image tumor hypoxia. See paragraph 39 of Exhibit A.

Therefore, Dr. Bryant has declared that "[o]ne of ordinary skill in the synthesis and use of radionuclide imaging agents, upon reading the specification, would have been able to make and

use the claimed radionuclide-labeled tumor hypoxia targeting ligand conjugates without an undue amount of experimentation." Paragraph 40 of Exhibit A. Furthermore, "[o]ne of ordinary skill in the synthesis and use of radionuclide imaging agents would have understood that a 'tumor hypoxia targeting ligand' refers to a member of a specific group of agents that can be readily identified, and that the claims of the invention particularly point out and distinctly claim the subject matter that is the invention." Paragraph 40 of Exhibit A.

f. Claims Pertaining to Agents that Mimic Glucose

Mr. Bryant has reviewed the specification, and has found that aspects of the present invention that include agents that mimic glucose as the tissue specific ligand are discussed throughout the specification. See paragraph 41 of Exhibit A. For example, the specification includes information pertaining to exemplary agents that mimic glucose, information pertaining to the conjugation chemistry of targeting ligands that can be applied to agents that mimic glucose, information pertaining to tumor glycolysis targeting, and two working examples pertaining to the synthesis of ^{99m}Tc-EC-neomycin and ^{99m}Tc-EC-deoxyglucose and their evaluation as imaging agents. See paragraph 41 of Exhibit A. The specification has also been found to provide substantial guidance pertaining to the preparation of EC-targeting ligand conjugates that can be applied to conjugates of EC with agents that mimic glucose, as well as information pertaining to the radionuclide labeling of these conjugates. See paragraph 42 of Exhibit A.

Mr. Bryant also notes that the phrase "an agent that mimics glucose" would have been understood to refer to specific compounds which target glucose metabolism, and that a substantial amount of information pertaining to such compounds was available around the priority date of the present patent application in the context of unrelated inventions. See paragraph 42 of Exhibit A. Exemplary agents that mimic glucose are set forth in paragraphs 43 and 44 of Exhibit A, and include [14C]deoxyglucose and ^{18}F-FDG. Certain of these agents, such

as FDG, had been widely used in nuclear medicine for cancer diagnosis. See paragraph 44 of Exhibit A. Aminoglycosides were known as agents that mimic glucose, and their use as ligands was well known. See paragraph 45 of Exhibit A.

In view of the above, Mr. Bryant has concluded that "a person of ordinary skill in the synthesis and use of radionuclide imaging agents, upon reading the specification, would have been able to make and use the claimed radionuclide-labeled conjugates incorporating agents that mimic glucose without an undue amount of experimentation." Paragraph 46 of Exhibit A. Furthermore, "one of ordinary skill in the synthesis and use of radionuclide imaging agents would have understood that an 'agent that mimics glucose' refers to a member of a specific group of agents that can be readily identified."

g. Conclusion

Mr. Bryant has declared that in view of the above, "claims 2-4, 6, 8-10, 15, 23, 30, 31, 33-35, and 37-41 of the above referenced patent application contains subject matter which was described in the specification of the above-referenced patent application in such a way as to enable one of ordinary skill in the synthesis and use of radionuclide imaging agents to make and use the invention." Paragraph 47 of Exhibit A. Furthermore, Mr. Bryant has declared that "[t]he description of the invention provided in the specification is sufficiently clear and concise such that one of ordinary skill in the synthesis and use of radionuclide imaging agents would be able to make the claimed agents and practice the claimed methods without an undue amount of experimentation." Paragraph 47 of Exhibit A. In addition, he has found that each of the groups set forth by the phrases "anticancer agent," "tumor marker," "folate receptor targeting ligand," "tumor apoptotic cell targeting ligand," "tumor hypoxia targeting ligand," and "an agent that mimics glucose" are limited, and members of these groups "can be identified using techniques known to those of ordinary skill in the synthesis and use of radionuclide imaging agents." Paragraph 47 of Exhibit A. He also notes that "the art pertaining to the synthesis and use of EC-

targeting ligand complexes was highly advanced at the time of filing of the application, and determining which types of targeting ligand complexes would bind EC and generate results would not have required an undue amount of experimentation." Paragraph 47 of Exhibit A. As a result, he observes, there would be predictability in practicing the claimed invention, particularly in view of the guidance provided by the working examples. See paragraph 47 of Exhibit A.

5. Conclusion

In view of the argumentation and evidence set forth above, Applicants respectfully request withdrawal of the enablement rejections under 35 U.S.C. §112, first paragraph.

G. Rejections based on 35 U.S.C. 112, second paragraph

The Action rejects claims 2-4, 6, 8, 10, 15, 23, 30, 31, 33-35, and 37-41 based on the premise that the phrases "anticancer agent," "tumor marker," "folate receptor targeting ligand," "tumor apoptotic cell targeting ligand," "tumor hypoxia targeting ligand," and "an agent that mimics glucose" are "unlimited." See Office Action dated September 29, 2003. Applicants respectfully traverse.

The phrases "anticancer agent," "tumor marker," "folate receptor targeting ligand," "tumor apoptotic cell targeting ligand," "tumor hypoxia targeting ligand," and "an agent that mimics glucose" are terms used to refer to specific classes of targeting ligands. Each class of targeting ligand, when taken in light of the description provided in the specification, is readily discernable to one of ordinary skill in the art.

1. Declaration of Jerry L. Bryant, M.S.

Applicant refers to the preceding discussion pertaining to the Declaration of Mr. Jerry Bryant related to ability of one of skill in the art to readily identify or obtain tissue specific ligands as described in the specification and in the art. As set forth in the Declaration, Mr. Bryant has an understanding of the nature of the present rejection pertaining to

indefiniteness. See paragraph 6 of Exhibit A. He has declared that "[t]he information provided in the specification would have permitted one skilled in the synthesis and use of radiolabeled imaging agents to understand that the phrases 'anticancer agent,' 'tumor marker,' 'folate receptor targeting ligand,' 'tumor apoptotic cell targeting ligand,' 'tumor hypoxia targeting ligand,' and 'an agent that mimics glucose' are generally accepted phrases that are used to refer to specific, defined classes of targeting ligands." Paragraph 10 of Exhibit A. In support of this conclusion, Mr. Bryant cites relevant sections of the specification and reference materials pertaining to unrelated inventions that were available at or around the time of the priority date. These sections of the specification and reference materials are discussed above in the response pertaining to the enablement rejections, and the discussion is herein specifically incorporated to apply to this section of the response. Additional detail is provided as follows.

a. Claims Drawn to Anticancer Agents

Regarding claims drawn to "anticancer agents" as targeting ligands for use in the present invention, Mr. Bryant, as set forth in the previous section, has cited relevant sections of the specification that disclose substantial information pertaining to anticancer agents, including numerous exemplary agents, such as those set forth in Table 2 of the specification. See paragraphs 12-14 of Exhibit A. He has also cited relevant reference material from unrelated inventions that was available at around the time of the priority date, including information pertaining to numerous anticancer agents that were known in the art, and their use as targeting ligands in unrelated inventions. See paragraphs 15-17 of Exhibit A. In view of this information, Mr. Bryant has declared that "[t]he phrase 'anticancer agent' [in the specification] would have been understood [by one of ordinary skill in the synthesis and use of radiolabeled imaging agents] to refer to agents such as chemotherapeutic drugs such as methotrexate, paclitaxel or tamoxifen, which had been widely used by scientists and clinicians for many years." Paragraph

15 of Exhibit A. Consequently, the claims of the invention "particularly point out and distinctly claim the subject matter that is the invention." Paragraph 18 of Exhibit A.

b. Claims Drawn to Tumor Markers

Regarding claims drawn to "tumor markers," Mr. Bryant, as set forth above, has identified substantial support in the specification pertaining to "tumor markers" as the tissue specific ligand for use in the present invention. Paragraphs 19-10 of Exhibit A. He has also, as set forth above, identified a substantial amount of reference material pertaining to tumor markers and their use as targeting ligands from around the time of the priority date of the above-referenced patent application in the context of unrelated inventions. Paragraph 21 of Exhibit A. Numerous tumor markers were known to exist in the art at around the time of the priority date (see paragraph 21 of Exhibit A), tumor markers were known to be used as targeting ligands in the context of unrelated inventions (see paragraph 22 of Exhibit A). In view of this information, Mr. Bryant has declared that "[o]ne of ordinary skill in the synthesis and use of radionuclide imaging agents would have understood that a 'tumor marker' refers to a member of a group of agents that can be readily identified by techniques such as Northern blot analysis, Western Blot analysis, and immunohistochemistry, and that the claims of the invention particularly point out and distinctly claim the subject matter that is the invention." See paragraph 23 of Exhibit A.

c. Claims Pertaining to Folate Receptor Targeting Ligands

Mr. Bryant, as previously detailed, has identified substantial support in the specification pertaining to folate receptor targeting ligands and the preparation of radiolabeled folate receptor targeting ligands. See paragraphs 24-25 of Exhibit A. This support includes exemplary folate receptor targeting ligands, as set forth on page 5, line 23 through page 7, line 1 of the specification. See paragraph 24 of Exhibit A.

Furthermore, as discussed above, Mr. Bryant has set forth in his Declaration a summary pertaining of the state-of-the-art regarding folate receptor targeting ligands that was known on or

about the time of the priority date of the present patent application in the context of unrelated inventions. See paragraph 27 of Exhibit A. Exemplary folate receptor targeting ligands that were known in the art at or around the priority date of the referenced patent application included folic acid, folinic acid, pteropolyglutamic acid, and folate receptor-binding pteridines such as tetrahydropterins, dihydrofolates, tetrahydrofolates, and their deaza and dideaza analogs. Paragraph 27 of Exhibit A, citing column 7, lines 28-34 of U.S. Patent 5,108,921 (Exhibit 35). Furthermore, folate had been used as a targeting ligand in a new tumor imaging agent. See paragraph 28 of Exhibit A. The information available pertaining to folate receptor targeting ligands demonstrates that "skill in the art was very high" in the context of unrelated inventions. Paragraph 28 of Exhibit A.

Mr. Bryant has declared that "[i]n view of the disclosure in the specification, one of ordinary skill in the synthesis and use of radionuclide imaging agents would have understood that a 'folate receptor targeting ligand' refers to a member of a group of agents that can be readily identified, and that the claims of the invention particularly point out and distinctly claim the subject matter that is the invention." Paragraph 29 of Exhibit A.

d. Claims Pertaining to Tumor Apoptotic Cell Targeting Ligands

As set forth above, Mr. Bryant has reviewed the instant specification, and has identified substantial guidance regarding aspects of the present invention that include a tumor apoptotic cell targeting ligand. See paragraph 30 of Exhibit A. For example, examples of tumor apoptotic cell targeting ligands can be found on page 5, lines 24-25, and a detailed discuss regarding the imaging of tumor apoptotic cells that includes exemplary tumor apoptotic cell targeting ligands such as annexin V can be found on page 28, lines 14-20 and page 29, lines 19-23. Furthermore, Example 4 of the specification pertains to the synthesis, biodistribution, and imaging studies of a radiolabeled conjugate that includes annexin V. See paragraph 30 of Exhibit A.

In addition, as set forth above, the state-of-the-art pertaining to tumor apoptotic cell targeting ligands in the context of unrelated inventions was well-established, and markers for apoptotis were actively under investigation. See paragraphs 32-33 of Exhibit A. Mr. Bryant declares that in view of the state-of-the-art, "[t]he phrase 'tumor apoptotic cell targeting ligand' would have been and should be well understood to refer to a very limited number of specific compounds which are capable of detecting the death of tumor cells." Paragraph 34 of Exhibit A. Exemplary tumor apoptotic cell targeting ligands were known in the art, such as PK11195 and annexin V. See paragraph 34 of Exhibit A.

Based on the state-of-the-art at or around the time of the priority date, Mr. Bryant declares that "one of ordinary skill in the synthesis and use of radionuclide imaging agents would have understood that an 'apoptotic cell targeting ligand' refers to a member of a specific group of agents that can be readily identified using techniques such as those set forth above, and that the claims of the invention particularly point out and distinctly claim the subject matter that is the invention." Paragraph 35 of Exhibit A.

e. Claims Pertaining to Tumor Hypoxia Targeting Ligands

As discussed in the response set forth above pertaining to enablement, Mr. Bryant has identified in-depth information in the specification pertaining to tumor hypoxia targeting ligands, and conjugates that include these types of targeting ligands. See Paragraph 36 of Exhibit A. As set forth in his Declaration, Mr. Bryant has identified exemplary tumor hypoxia targeting ligands in the specification, such as those set forth on page 5, lines 24-25 of the specification. See paragraph 36 of Exhibit A. In addition, the specification includes a detailed discussion pertaining to the assessment of tumor hypoxia by imaging, information pertaining to the imaging of hypoxia due to stroke using ^{99m}Tc-EC-metronidazole, and information regarding the preparation of EC-tumor hypoxia targeting ligand conjugates. See paragraphs 36 and 37 of Exhibit A.

Furthermore, as set forth above, the state-of-the-art pertaining to tumor hypoxia targeting ligands was well-established in the context of unrelated inventions. See paragraph 38 of Exhibit A. A number of hypoxia-selective antitumor agents had been identified, such as bis(nitroimidazolyl)alkanecarboxamides, adrenomedullin, and fluorine-18-fluoromisonidazole. See paragraph 28 of Exhibit A. Furthermore, Yang *et al.*, 1999b (Exhibit 57 of Exhibit A, a publication of the inventors) had developed a ^{99m}Tc-labeled metronidazole using EC as a chelator, and determined that it was feasible to use this agent to image tumor hypoxia. See paragraph 39 of Exhibit A. Thus, Mr. Bryant has declared that "use of tumor markers as targeting ligands was well-established, and the level of expertise of those in this field was high." Paragraph 39 of Exhibit A.

In view of the state-of-the-art pertaining to tumor hypoxia targeting ligands, Mr. Bryant has declared that upon reading the specification, "[o]ne of ordinary skill in the synthesis and use of radionuclide imaging agents would have understood that a 'tumor hypoxia targeting ligand' refers to a member of a specific group of agents that can be readily identified, and that the claims of the invention particularly point out and distinctly claim the subject matter that is the invention." Paragraph 40 of Exhibit A.

f. Claims Pertaining to Agents that Mimic Glucose

As set forth previously, Mr. Bryant has reviewed the specification and has identified information pertaining to agents that mimic glucose and their use as targeting ligands throughout the specification. For example, exemplary agents that mimic glucose can be found on page 5, line 29 through page 6, line 3. See paragraph 41 of Exhibit A. The specification also includes detailed information pertaining to the conjugation chemistry of these targeting ligands, a discussion regarding tumor glycolysis targeting, and working examples pertaining to ^{99m}Tc-EC-neomycin and ^{99m}Tc-EC-deoxyglucose. See paragraphs 41-42 of Exhibit A.

Furthermore, as set forth above, Mr. Bryant has reviewed the state-of-the-art pertaining to agents that mimic glucose on or about the priority date of the referenced patent application in the context of other inventions, and has determined that the state-of-the-art in this area was well-established. See paragraph 43 of Exhibit A. Agents that mimic glucose were established agents in the diagnosis and treatment of cancer. See paragraph 43 of Exhibit A. Exemplary agents that mimic glucose that were known in the art included [14C]deoxyglucose, ^{18}F-FDG, glucose-6-phosphate, 2-deoxyglucose-6-phosphate, glucosamine-6-phosphate, N-acetylglucosamine-6-phosphate, and aminoglycosides. See paragraph 44 of Exhibit A.

Therefore, Mr. Bryant declares that a person of ordinary skill in the synthesis and use of radionuclide imaging agents, upon reading the specification, would have understood that 'an agent that mimics glucose' refers to a member of a specific group of agents that can be readily identified, and that the claims of the invention particularly point out and distinctly claim the subject matter that is the invention." Paragraph 46 of Exhibit A.

g. Conclusion

Based on his review of the specification and in view of the reference material available at or around the priority date of the patent application pertaining to the phrases "anticancer agent," "tumor marker," "folate receptor targeting ligand," "tumor apoptotic cell targeting ligand," "tumor hypoxia targeting ligand," and "an agent that mimics glucose," Mr. Bryant declares that "the present claims particularly point out and distinctly claim the subject matter that the inventors believe is the invention." Paragraph 48 of Exhibit A. He further declares that "the phrases 'anticancer agent,' 'tumor marker,' 'folate receptor targeting ligand,' 'tumor apoptotic cell targeting ligand,' 'tumor hypoxia targeting ligand,' and 'an agent that mimics glucocose' are not confusing, nor are they unlimited in their scope," and that "someone skilled in the art would not and should not be confused by what these phrases mean." Paragraph 48 of Exhibit A. He further declares that "these phrases are definite because they refer to specific classes of targeting

ligands whose members can be identified using techniques well-known to those who have an understanding of the synthesis and use of radionuclide imaging agents." Paragraph 48 of Exhibit A.

2. Breadth of a Claim is not to be Equated with Indefiniteness

By indicating that the phrases "anticancer agent," "tumor marker," "folate receptor targeting ligand," "tumor apoptotic cell targeting ligand," "tumor hypoxia targeting ligand," and "an agent that mimics glucose" are unlimited, the Examiner appears to be equating breadth of the claim to indefiniteness. However, "[b]readth of a claim is not to be equated with indefiniteness." *MPEP* §2173.04, citing *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). "If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. §112, second paragraph. As per the above argumentation and evidence, Applicants have demonstrated that the scope of the subject matter embraced by the claims is sufficiently clear such that the claims particularly point out and distinctly claim the subject matter that is the invention. As discussed above, the phrases at issue in this rejection pertain to different classes of targeting ligands that can be identified using techniques that were generally available to those of ordinary skill in the synthesis and use of radionuclide imaging agents, and thus are not unlimited in scope.

3. Conclusion

Definiteness of claim language must be analyzed, not only based on the content of the particular application disclosure and teachings of the prior art, but also on "[t]he claims interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made." *MPEP* §2173.02. Based on the Declaration of Jerry L.

Bryant, M.S. set forth herein, the phrases "anticancer agent," "tumor marker," "folate receptor targeting ligand," "tumor apoptotic cell targeting ligand," "tumor hypoxia targeting ligand," and "an agent that mimics glucose" are clear, and set forth defined subsets of tissue-specific ligands. Further, Applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims.

In view of the argumentation and evidence set forth above, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §112, second paragraph.

H. Rejection of Claim 32 based on 35 U.S.C. 112, second paragraph

The Action maintains the 112, second paragraph, rejection in part, with respect to the term "octreotide."

Applicants do not understand the rejection and thus maintain claim 32 as filed. The drug "octreotide" is a well-known octopeptide used to treat cancer. See enclosed product description. Thus, it falls in the class of anticancer agents and is identified as such in the present application in Table 2 at page 36. The Action states that art was previously cited against peptides. Applicants are unaware to what the Examiner refers. However, the relevancy of this, whether true or not, to the present §112, second paragraph, rejection is unclear. There is no question that the term "octreotide" is sufficiently clear and unabiguous.

I. Conclusions

Applicants have submitted remarks which are believed to place the present claims in condition for allowance. In view of this, Applicants respectfully request that the present claims be passed for allowance.

EXHIBIT A

CERTIFICATE OF MAILING
37 C.F.R. 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, on the date below:

12/23/04 (Date) — Monica A. De La Paz

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Yang, *et al.*

Serial No.: 09/599,152

Filed: June 21, 2000

For: ETHYLENEDICYSTEINE (EC)-DRUG CONJUGATES, COMPOSITIONS AND METHODS FOR TISSUE SPECIFIC DISEASE IMAGING

Group Art Unit: 1619

Examiner: Jones, D.

Atty. Dkt. No.: UTXC:664

DECLARATION OF JERRY L. BRYANT, M.S., UNDER 37 C.F.R. §1.132

MS AF
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

I, Jerry L. Bryant, M.S., do declare that:

1. I am a United States citizen residing at 6861 Staffordshire St. Houston, TX 77030.

2. I currently hold the position of Chief Technology Officer, Head of Scientific Evaluation, Division of Business Development, Cell>Point, LLC, 7120 E. Orchard Road, Suite 350, Englewood, CO 80111. A copy of my curriculum vitae, including a list of my publications, is attached as Appendix A.

3. I am skilled in the synthesis and use of radionuclide-labeled imaging agents, as evidenced by the following:

- I have worked as Chief Technology Officer of Cell>Point, LLC since 2001.
- I have been employed as the Director of Research Development of VeriMed Research Corporation in Houston, TX, from 2002-2004.
- My duties at Cell>Point and VeriMed include participation in the development of novel radiopharmaceuticals for different diseases, such as cancer, cardiovascular disease, and diabetes. I have also been involved with studies directed to the synthesis and use of radionuclides, and studies directed to understanding the mechanism and biochemistry of the agents as it pertains to the pharmacokinetics and biodistribution of the agents in animals and humans. In addition, I have been involved in the evaluation of new technologies for the treatment of cancer, cardiovascular disease, and diabetes.
- I was employed as Chief Scientific Officer of Allcure, Inc., in Houston, TX, from May, 2001-May, 2002. My duties at Allcure included designing and marketing *in vitro* and *in vivo* services to drug and bio-tech companies for evaluating compounds of interest (nuclear medicine, SCID mouse *in vivo* service and mechanism studies).
- I have experience as a Research Assistant II in the Department of Nuclear Medicine, the Division of Diagnostic Imaging, of the University of Texas M.D. Anderson Cancer Center, from October, 2002 to June, 2003.
- I am a co-inventor of three patent applications that pertain to imaging technology, including USSN 10/703,405 ("Ethylenedicysteine (EC)-Drug Conjugates, Compositions, and Methods for Tissue Specific Disease Imaging," Yang *et al.*); USSN 10/942,615 ("Mechanism-Based Targeted Pancreatic Beta Cell Imaging and Therapy," Yang *et al.*);

and USSN 10/732,919 (N2S2 Chelate-Targeting Ligand Conjugates," Yang *et al.*). See page 6 of Appendix A.

- I have been involved in funded studies pertaining to the development and evaluation of imaging agents during the past five years, including: (1) a study of CT and MRI functional agent development and evaluation supported by VeriMed Research Corporation; (2) a study of 99m-Tc-Ethylenedicysteine (EC)-Drug Conjugates for Tissue Specific Disease Imaging supported by Cell>Point, LLC; and (3) a study to compare Tc-99m-EC-deoxyglucose (EC-DG) and FDG-PET scans for the evaluation of patients suspected of having persistent/recurrent squamous cell carcinoma of the larynx after definitive treatment with radiation therapy and the evaluation of primary lung cancer patients, sponsored by Cell>Point, LLC. See page 7 of Appendix A.
- I am a co-author of seven articles and numerous abstracts pertaining to the evaluation and testing of radiolabeled imaging agents. See pages 9-14 of Appendix A.
- I am also a co-author of two book chapters pertaining to radiolabeled imaging agents and their uses in chemistry and nuclear medicine. See page 14 of Appendix A.
- Regarding my formal education, I have a Master of Science degree (1991) in Microbiology & Cell Science and Molecular Biology from the University of Florida, and a B.S. degree (1987) in Chemistry and Biochemistry from Tennessee State University.
- I have extensive experience in cell and molecular biology, as delineated in my curriculum vitae. See pages 2-3, Appendix A.

4. I have reviewed the above-referenced application, as well as the Office Actions to the above-referenced application that are dated September 29, 2003, and June 25, 2004. I understand that the above-referenced application was filed on or about June 21, 2000.

5. I understand that the Examiner has rejected claims 2-4, 6, 8-10, 15, 23, 30, 31, 33-35, and 37-41 of the above-referenced application because the Examiner believes the claims contain subject matter that was not described in the specification in such a way as to enable a skilled expert in the synthesis of radionuclide-labeled imaging agents to make and use the invention. I understand that the Examiner believes this to be true because she considers the potential number of EC-targeting ligand complexes to be too vast since the phrases "anticancer agent," "tumor marker," "folate receptor targeting ligand," "tumor apoptotic cell targeting ligand," "tumor hypoxia targeting ligand," and "an agent that mimics glucose" are said to be unlimited. I also understand that the Examiner believes the art pertaining to the synthesis of ethylenedicysteine (EC)-targeting ligand complexes is highly unpredictable, and determining which types of targeting ligands would bind EC and generate results would require an undue amount of experimentation such that there would be little predictability in practicing the claimed invention. In addition, the examples presented in the specification are considered by the Examiner to be insufficient to enable the public to prepare the claimed EC-targeting ligand complexes. I respectfully disagree for the reasons set forth below.

6. I also understand that the Examiner has rejected claims 2-4, 6, 8-10, 15, 23, 30, 31, 33-35, and 37-41 of the above-referenced application because the Examiner believes that the claims are indefinite because they do not particularly point out and distinctly claim the subject matter that the inventors believe is their invention. In particular, the Examiner is of the opinion that the claims are confusing because the phrases "anticancer agent," "tumor marker," "folate receptor targeting ligand," "tumor apoptotic cell targeting

ligand," "tumor hypoxia targeting ligand," and "an agent that mimics glucose" are considered unlimited. I again respectfully disagree for the reasons set forth below.

7. As a scientist who has worked in translational medicine, the technology disclosed in the above-referenced patent application will serve as the foundation for the development of novel diagnostic and therapeutic radiopharmaceuticals. A single technology with the capability to simplify the ease of radiolabeling of an array of tissue specific ligands has not been available to scientists and clinicians who work in the field of nuclear oncology, nuclear cardiology and infectious disease. It is important to note that the chemistry of the claimed technology is such that a skilled expert in the synthesis of radionuclide-labeled imaging agents, with the availability of the present specification, will be able to make and use the invention without undue experimentation.

8. The beauty of this technology is its ease of use. Even the most average of skilled experts should have no difficulty making and using the invention when presented with the information in the present specification. It is well known that scientists and clinicians working in oncology, cardiology and infectious disease have had a very keen interest in tissue specific radiolabeled ligands that can be used to identify specific tissue type(s) in an *in vivo* model.

9. Without reservation, I believe that if a skilled expert had the foresight to invent and develop this technology many years ago, it would be in routine use by scientists in the laboratory and clinicians in the hospital. With access to the information set forth in the present specification, I have no doubt that a skilled expert in the synthesis of

radionuclide-labeled imaging agents can easily and conveniently make and use the invention for their specific field of interest.

10. One skilled in the synthesis and use of radionuclide imaging agents would have been enabled to make and use the claimed invention when presented with the information provided in the specification. The information provided in the specification would have permitted one skilled in the synthesis and use of radiolabeled imaging agents to understand that the phrases "anticancer agent," "tumor marker," "folate receptor targeting ligand," "tumor apoptotic cell targeting ligand," "tumor hypoxia targeting ligand," and "an agent that mimics glucose" are generally accepted phrases that are used to refer to specific, defined classes of targeting ligands. One skilled in the synthesis and use of radionuclide imaging agents would have no difficulty making and using the claimed invention when presented with the information provided in the specification. By utilizing the claimed technology, a skilled expert would be able to build upon their existing knowledge to develop better radiolabeled imaging agents for genetic diseases and other human diseases. Therefore, the specification, with its numerous working examples, provides sufficient guidance to one of skill in the synthesis of radionuclide imaging agents to predictably identify the EC-targeting ligand complexes of the invention without an undue amount of experimentation.

11. The cited sections of the specification and reference materials set forth beginning with paragraph 12 below provide facts in support of my assessment. In particular, these cited sections of the specification and reference materials support my conclusions regarding the general use and understanding of the phrases "anticancer agent," "tumor marker,"

"folate receptor targeting ligand," "tumor apoptotic cell targeting ligand," "tumor hypoxia targeting ligand," and "an agent that mimics glucose," and the fact that EC-targeting ligands of the present invention that incorporate an "anticancer agent," a "tumor marker," a "folate receptor targeting ligand," a "tumor apoptotic cell targeting ligand," a "tumor hypoxia targeting ligand," or "an agent that mimics glucose" can be made and used without an undue amount of experimentation.

12. Claims Pertaining to Anticancer Agents

Support in the Specification

The entire specification provides a substantial amount of detail regarding embodiments of the claimed invention where the tissue specific ligand is an anticancer agent. Particular sections of the specification that are exemplary include page 5, lines 16-18, which provides examples of anticancer agents to be used in the claimed EC-targeting ligand complexes and page 9, lines 18-24 which indicates that examples of anticancer agents include chemotherapeutic agents used in the treatment of cancer. A listing of exemplary anticancer drugs is provided in Table 2 (page 34, line 24 through page 42, line 2).

13. Information pertaining to the conjugation chemistry of anticancer agents and additional examples of anticancer agents for use in the invention are provided on page 6, lines 4-16 and on page 22, lines 18 through page 23, line 21. The specification also provides substantial guidance pertaining to the preparation of EC-targeting ligand derivatives (see, *e.g.*, page 7, lines 5-13 and page 20, lines 7-15), and the radionuclide labeling of these EC-targeting ligand derivatives (see, *e.g.*, page 7, lines 15-20 and page 7, line 17 through

page 22, line 16; page 21, line 6 through page 22, line 16; page 23, line 23 through page 24, line 16).

14. Examples of radiolabeled ligands of the present invention where the targeting ligand is an anticancer agent are provided on page 6, line 30 through page 7, line 4, and Table 1, page 23. Information pertaining to the synthesis, biodistribution, and imaging properties of ^{99m}TC-EC-methotrexate and ^{99m}Tc-EC-tomudex are discussed in Example 1 (page 32, line 10 through page 45, line 7) and FIGS. 2 and 3 . Information pertaining to the synthesis, biodistribution, and imaging properties of ^{99m}TC-EC-colchicine is discussed in Example 5 (page 56, line 11 through page 60, line 17), FIGS. 21-27, and Tables 6 and 7.

15. *Reference Materials Available Around the Time of the Priority Date*

Around the time of the priority date, numerous anticancer agents were known and widely used in the treatment of cancer. See, *e.g.*, review in Connors, 1996 (Exhibit 1). I*n vitro* studies, animal protocols, and clinical trials, were evaluation tools commonly used to assist in the identification of anticancer agents. Reviewed in Connors, 1996 (Exhibit 1). Exemplary *in vitro* studies that were known to be useful in the identification of anticancer agents included cancer cell growth inhibition studies (see, *e.g.*, Jiang *et al.* (Exhibit 2), 1983; Jiang *et al.*, 1998 (Exhibit 3); Palyl *et al.*, 1999 (Exhibit 4), and Yoshinari *et al.*, 1999 (Exhibit 5); U.S. Patent 5,356,793 (Exhibit 6); Yamori *et al.*, 1999 (Exhibit 7)). *In vivo* studies to evaluate anticancer agents ranged from human cancer xenografts in nude mice (see, *e.g.*, Cammisuli *et al.*, 1996 (Exhibit 8) and Hjarnaa *et al.*, 1999 (Exhibit 9); Yamori *et al.*, 1999 (Exhibit 7)) and other tumor-bearing animal studies (see, *e.g.*, Cafaggi *et al.*, 1992; Exhibit 10) to clinical trials involving patients afflicted

with cancer (reviewed in Connors, 1996 (Exhibit 1); see, *e.g.*, Foa *et al.*, 1994 (Exhibit 11)). The chemical and physical properties of many of these agents were well-understood. See, *e.g.*, Pavlik *et al.*, 1983 (Exhibit 12). Thus, one of skill in the synthesis and use of radionuclide agents for imaging would have understood that numerous anticancer agents were known to be in existence, and numerous commonly available laboratory and clinical investigative techniques were available to assist in the identification of new anticancer agents. The phrase "anticancer agent" would have been understood to refer to agents such as chemotherapeutic drugs such as methotrexate, paclitaxel or tamoxifen, which had been widely used by scientists and clinicians for many years.

16. Furthermore, the use of anticancer agents as targeting ligands was well-known at around the time the application was filed in the context of unrelated inventions. For example, WO98/08859 (Exhibit 13) described bioconjugates of a bioactive agent and an organocobalt complex, where certain aspects of the invention involved an anticancer agent as the bioactive agent. See abstract. In Chakrabarti *et al.*, 1998 (Exhibit 14), the antitumor antibiotic chromomycin A3 was reported to be a "DNA-binding ligand." See abstract. Immunoconjugates that included an antibody fragment covalently bound to a diagnostic or therapeutic agent, such as an anticancer agent, were described in U.S. Patent 5,635,603 (Exhibit 15). Conjugation of the anticancer agent gemcitabine to agents that target peripheral benzodiazepine receptors in tumors was described by Guo and Gallo (1999) (Exhibit 16).

17. I am aware of publications of the present inventors wherein anticancer agents were used as targeting ligands in conjugates for imaging. For example, Inoue *et al.* (1999) (Exhibit 17) disclosed ^{111}In-DTPA-paclitaxel conjugates for use in scintigraphy. Zareneyrizi *et al.*, 1999 (Exhibit 18) described the use of ^{99m}Tc-EC-colchicine for imaging studies, and Yang *et al.*, 1999a (Exhibit 19) described synthesis of ^{111}In-labeled DTPA-methotrexate for use in imaging studies. One of ordinary skill in the synthesis and use of radiolabeled imaging agents would have understood that paclitaxel, colchicine, and methotrexate are exemplary anticancer agents that can be incorporated as targeting ligands into the conjugates of the claimed invention. Furthermore, one of ordinary skill in the art would have understand that these publications, which pertain to the synthesis of radiolabled conjugates, would provide background information to one of ordinary skill in the art which would enable a person of skill in the art, upon reading the specification, to practice the claimed invention without an undue amount of experimentation.

18. Therefore, one skilled in the synthesis and use of radiolabeled imaging agents would have understood, from reading the specification, that an "anticancer agent" is a phrase used to refer to a member of a specific group of agents that can be readily identified by *in vitro* and/or *in vivo* studies, such as the examples set forth above. In addition, one of ordinary skill in the synthesis of radionuclide imaging agents would have also understood that "anticancer agents" can be used as ligands. The cited references demonstrate that the state-of-the-art pertaining to the use of "anticancer agents" as ligands was highly-developed. As a result, one of ordinary skill in the synthesis and use of radionuclide imaging agents, upon reading the specification of the present application, would have been able to make and use the claimed radionuclide-labeled anticancer agents without an

undue amount of experimentation. Consequently, the claims of the invention particularly point out and distinctly claim the subject matter that is the invention.

19. Claims Pertaining to Tumor Markers

Support in the Specification

Aspects of the present invention that include a tumor marker as the tissue-specific ligand are addressed throughout the specification. For example, a general discussion concerning the use of tumor markers as tissue specific ligands can be found on page 5, lines 5-14. A list of examples of tumor markers can be found on page 5, lines 22, where it is noted that "[i]t is envisioned that any other known tumor marker or any monoclonal antibody will be effective for use in conjunction with the invention." Additional examples of tumor markers for use in the conjugates of the present invention are included in claim 9.

20. The specification provides substantial guidance regarding the synthesis of radiolabeled EC-targeting ligand derivatives. In particular, information concerning the conjugation chemistry of ligands such as tumor markers of the present invention can be found on page 22, line 18 through page 23, line 21. The specification also provides substantial guidance pertaining to the preparation of EC-targeting ligand derivatives (see, *e.g.*, page 7, lines 5-13 and page 20, lines 7-15), and the radionuclide labeling of these EC-targeting ligand derivatives (see, *e.g.*, page 7, lines 15-20 and page 7, line 17 through page 22, line 16; page 21, line 6 through page 22, line 16; page 23, line 23 through page 24, line 16). Information pertaining to the synthesis, biodistribution, and imaging properties of exemplary ^{99m}Tc-EC-targeting ligand derivatives is found in Examples 1-7 (page 32, line 10 through page 68, line 12).

21. *Reference Materials Available Around the Time of the Priority Date*

Around the time of the priority date of the referenced patent application, the state-of-the-art pertaining to tumor markers and their use as targeting ligands was a developing area of technology in the context of unrelated inventions. In particular, numerous tumor markers had been identified. For example, identification of a candidate tumor marker, PGP9.5, was described in Hibi *et al.*, 1999 (Exhibit 20). Experimental techniques used to identify tumor markers in Hibi *et al.* (Exhibit 20) included Northern blot analysis, Western blot analysis, and immunohistochemical staining. In Becker *et al.*, 1999 (Exhibit 21), *in vitro* studies using Western blotting and immunohistochemistry of E-cadherin transfected cells were employed to identify a mutated E-cadherin gene as a tumor marker. In Pavicevic *et al.*, 1998 (Exhibit 22), enzyme immunoassays were used to identify CYFRA 21-1 as a serum tumor marker in lung cancer. Immunohistochemistry was also used to identify the association of matrix metalloproteinase-1 with poor prognosis in esophageal cancer (Murray *et al.*, 1998; Exhibit 23), and the association of tryptophan hydroxylase antibodies with carcinoid (Meyer *et al.*, 1998; Exhibit 24).

22. Prior to the priority date, tumor markers were used in various contexts as targeting ligands. U.S. Patent 4,988,496 (Exhibit 25) disclosed chelate-targeting agent conjugates wherein the targeting agent ligand is a monoclonal antibody directed against an antigen on a tumor cell. See claims 3, 5, 6, and 7 of Exhibit 25. U.S. Patent 4,824,659 (Exhibit 26) disclosed modified antibodies that can bind a ligand, wherein the ligand in certain aspects of the invention is a marker which is produced by or associated with a tumor or a pathological lesion. (see claim 5). U.S. Patent 5,877,289 (Exhibit 27), which pertained to

methods and compositions for use in the coagulation of blood vessels, described agents that "bind to a tumor cell" as targeting ligands. Page 5, column 1, lines 10-14. U.S. Patent 5,013,556 (Exhibit 28) disclosed compositions of liposomes with enhanced circulation times, which in certain embodiments included surface-bound targeting ligands that could be specific antibodies directed against tumor-specific antigens. See claims 15 and 29. Lundberg *et al.* (1999) (Exhibit 29) described the conjugation of an anti-B-cell lymphoma monoclonal antibody to the surface of lipid-emulsion globules using a novel coupling agent. I am aware that a publication of the inventors, Kim *et al.*, 2000 (Exhibit 30) disclosed ^{99m}Tc-EC-polyglutamate in an effort to target glutamate receptors, which were known to be overexpressed in certain tumors. One of ordinary skill in the synthesis and use of radiolabeled imaging agents would have understood, from reading Kim *et al.*, 2000 (Exhibit 30) that polyglutamate is an example of a tumor marker ligand that could be incorporated into the conjugates of the claimed invention. In view of the background information provided in publications such as Kim *et al.*, 2000 (Exhibit 30) and the other publications set forth above, one of ordinary skill in the synthesis and use of radiolabeled imaging conjugates, upon reading the specification, would have been able to make and use the claimed radiolabeled conjugates without an undue amount of experimentation. It would follow that one of ordinary skill in the synthesis and use of radiolabeled contrast agents would have understood that tumor markers were actively used as targeting ligands at around the time of the priority date, and the state-of-the art was well-established.

23. In view of the information provided in the specification, one of ordinary skill in the synthesis and use of radionuclide imaging agents would have been able to make and use the claimed radionuclide-labeled tumor marker conjugates of the present invention

without an undue amount of experimentation. One of ordinary skill in the synthesis and use of radionuclide imaging agents would have understood that a "tumor marker" refers to a member of a group of agents that can be readily identified by techniques such as Northern blot analysis, Western Blot analysis, and immunohistochemistry, and that the claims of the invention particularly point out and distinctly claim the subject matter that is the invention.

24. Claims Pertaining to Folate Receptor Targeting Ligands

Support in the Specification

The specification provides detailed information pertaining to folate receptor targeting ligands and the preparation of radiolabeled folate receptor targeting ligands. Exemplary folate receptor targeting ligands are provided on page 5, line 23 and page 7, line 1. Information regarding the conjugation chemistry of targeting ligands, including folate receptor targeting ligands, is provided on page 6, lines 4-19 and page 22, line 18 through page 23, line 21. A detailed discussion pertaining to folate receptor targeting can be found on page 25, line 28 through page 26, line 27.

25. The specification also provides substantial guidance pertaining to the preparation of EC-targeting ligand derivatives (see, *e.g.*, page 7, lines 5-13 and page 20, lines 7-15), and the radionuclide labeling of these EC-targeting ligand derivatives (see, *e.g.*, page 7, lines 15-20 and page 7, line 17 through page 22, line 16; page 21, line 6 through page 22, line 16; page 23, line 23 through page 24, line 16) that can be applied in the preparation of radiolabeled EC-folate receptor targeting ligand derivatives. In addition, Example 1 and FIGS. 1-6 includes information regarding the synthesis, biodistribution and imaging

studies pertaining to ^{99m}Tc-EC-folate, ^{99m}Tc-EC-MTX, and ^{99m}Tc-EC-TDX. Page 32, line 10 through page 45, line 7.

26. *Reference Materials Available Around the Time of the Priority Date*

Around the priority date of the referenced patent application, there was a substantial amount of information pertaining to folate receptors and folate receptor targeting ligands in the context of unrelated inventions. The structure of the folate receptor, molecular and biochemical aspects of the folate receptor, and transport of agents across the folate receptor were established areas of research. Reviewed in Antony, 1996 (Exhibit 31); see also Holm *et al.*, 1994 (Exhibit 32), pertaining to the folate receptor of human mammary adenocarcinoma and Westerhof *et al.*, 1991 (Exhibit 33) pertaining to membrane transport of natural folates and antifolate compounds in murine leukemia cells. It was known that marked overexpression of folate receptors in some malignant cells suggested that the folate receptor may be an important target for diagnostic or therapeutic exploitation.

27. In addition, folate analogs were used in various contexts as targeting ligands. In particular, Sudimack *et al.*, 2000 (Exhibit 34) addressed mechanisms of targeted drug delivery via the folate receptor, including "coupling [of the drug] to a high affinity ligand, folic acid." Abstract, page 147. The abstract notes that folic acid is "a high affinity ligand of the folate receptor," and "folate conjugation, therefore, presents an alternative method of targeting the folate receptor." Abstract, page 147. U.S. Patent 5,108,921 (Exhibit 35), U.S. Patent 5,416,016 (Exhibit 36), and U.S. Patent 5,820,847 (Exhibit 37) described methods of enhanced transmembrane transport of molecule complexes of an

agent and a targeting ligand, where, in certain embodiments, the targeting ligands are folate analogs and other folate receptor-binding ligands. See Abstract and claim 1 in these patents. Examples of folate receptor targeting ligands presented in these patents include folic acid, folinic acid, pteropolyglutamic acid, and folate receptor-binding pteridines such as tetrahydropterins, dihydrofolates, tetrahydrofolates, and their deaza and dideaza analogs. See, *e.g.*, column 7, lines 28-34 of U.S. Patent 5,108,921 (Exhibit 35). U.S. Patent 5,891,468 (Exhibit 38) pertains to fusogenic liposome compositions that in certain aspects include, in certain embodiments, a targeting ligand such as folate attached to a hydrophilic polymer chain. See abstract and claims 1, 8, and 9. U.S Patent 6,033,884 (Exhibit 39) pertains to nucleic acid transporter systems for delivery of nucleic acid to a cell, where the transporter system contains a binding molecule covalently linked to a surface targeting ligand, such as folate. See abstract and claims 1, 3, and 4.

28. Regarding the development and use of radiolabeled agents for imaging, in 1998, ^{99m}Tc-ethylenedicysteine-folate was described as a new tumor imaging agent in a publication of the inventors. Ilgan *et al.*, 1998 (Exhibit 40). One of ordinary skill in the art would have understood that in view of the background information provided in Ilgan *et al.* and the other publications set forth above, one of ordinary skill in the synthesis and use of radiolabeled imaging conjugates, upon reading the specification, would have been able to make and use the claimed imaging conjugates without an undue amount of experimentation. These publications demonstrate that the state of the art as to folate receptor targeting and use of folate receptor as targeting ligands was well-developed, and skill in the art was very high.

29. In view of the disclosure in the specification, one of ordinary skill in the synthesis and use of radionuclide imaging agents, upon reading the specification, would have been able to make and use the claimed radionuclide-labeled folate receptor targeting ligand conjugates of the present invention without an undue amount of experimentation. One of ordinary skill in the synthesis and use of radionuclide imaging agents would have understood that a "folate receptor targeting ligand" refers to a member of a group of agents that can be readily identified, and that the claims of the invention particularly point out and distinctly claim the subject matter that is the invention.

30. Claims Pertaining to Tumor Apoptotic Cell Targeting Ligands

Support in the Specification

The specification provides substantial guidance regarding aspects of the invention that include a tumor apoptotic cell targeting ligand. In particular, page 5, lines 24-25 provide specific examples of the tumor apoptotic cell targeting ligands. Information pertaining to the conjugation chemistry of ligands, including tumor apoptotic cell targeting ligands, is provide on page 22, line 18 through page 23, line 21. A discussion regarding the imaging of tumor apoptotic cells, which includes an example of tumor apoptotic cell targeting ligands (annexin V), can be found on page 28, lines 14-20 and page 29, lines 19-23. Example 4 (page 54, line 24 through page 56, line 8) and FIGS. 18-20 provide information pertaining to the synthesis, biodistribution, and imaging studies of a radiolabeled conjugate that includes annexin-V, a tumor apoptotic cell targeting ligand.

31. The specification also provides substantial guidance pertaining to the preparation of EC-targeting ligand conjugates (see, *e.g.*, page 7, lines 5-13 and page 20, lines 7-15), and the

radionuclide labeling of these EC-targeting ligand derivatives (see, *e.g.*, page 7, lines 15-20 and page 7, line 17 through page 22, line 16; page 21, line 6 through page 22, line 16; page 23, line 23 through page 24, line 16). This information can be directly applied in the synthesis of radiolabeled EC-tumor apoptotic cell targeting ligand conjugates.

32. *Reference Materials Available Around the Time of the Priority Date*

At around the time of the priority date of the present patent application, it was well-established that apoptosis plays a critical role in the physiology of cancer. Reviewed in Thompson, 1995 (Exhibit 41). The cascade of cellular events that occur during apoptosis, and the search for markers for apoptosis was an established area of research. Reviewed in Blankenberg *et al.*, 1998 (Exhibit 42).

33. Markers for apoptosis were actively under investigation in the context of unrelated inventions. For example, i*n vitro* assays had been developed that use annexin V to detect apoptosis in a wide variety of cell types (see, *e.g.*, Boersma *et al.*, 1996 (Exhibit 43); Reutelingsperger and van Heerde, 1997 (Exhibit 44)). Using the RNAse protection assays and western blotting assays, Takamizawa *et al.*, 2000 (Exhibit 45), investigated the expression of apoptotic proteins by evaluating apoptotic mRNA species in tumor specimens.

34. The phrase "tumor apoptotic cell targeting ligand" would have been and should be well understood to refer to a very limited number of specific compounds which are capable of detecting the death of tumor cells. A number of apoptotic cell targeting ligands had been identified. For example, PK11195, a ligand of the mitochondrial benzodiazepine

receptor, was found to facilitate the induction of apoptosis of cells *in vitro* (Hirsch *et al.*, 1998; Exhibit 46). Annexin V, certainly the most well known and widely used tumor apoptotic ligand, had been identified as an apoptotic targeting ligand for radioimaging by Blankenberg *et al.* (1998) (Exhibit 42), who demonstrated that ^{99m}Tc-hydrazinonicotinamide-annexin V could be used to detect and serially image tissues and organs undergoing programmed cell death.. Parallel work by van den Eijnde *et al.*, 1997 (Exhibit 47), supported the use of annexin V for *in situ* detection of apoptotic cells in developing embryos using immunohistochemical techniques. Scientists around the world had been working with annexin V for a number of years as of the priority date. Furthermore, studies using cell culture techniques were underway to elucidate the role of Fas ligand in anticancer drug-mediated apoptosis. (see, *e.g.*, Tolomeo *et al.*, 1998 (Exhibit 48); McGahon *et al.*, 1998 (Exhibit 49)). Therefore, the state-of-the-art related to apoptotic cell targeting ligands was well-established. U.S. Patent 5,834,266 (Exhibit 50) and U.S. Patent 6,054,436 (Exhibit 51) pertain to methods of initiating apoptosis in genetically engineered cells using chimeric proteins capable of cross-linking ligands. See abstract and claim 1 in both patents.

35. Based on the above, one of ordinary skill in the synthesis and use of radionuclide imaging agents, upon reading the specification, would have been able to make and use the claimed radionuclide-labeled apoptotic cell targeting ligand conjugates without an undue amount of experimentation. Furthermore, one of ordinary skill in the synthesis and use of radionuclide imaging agents would have understood that an "apoptotic cell targeting ligand" refers to a member of a specific group of agents that can be readily identified

using techniques such as those set forth above, and that the claims of the invention particularly point out and distinctly claim the subject matter that is the invention.

36. Claims Pertaining to Tumor Hypoxia Targeting Ligands

Specification

The specification provides in-depth information pertaining to aspects of the invention that include tumor hypoxia targeting ligands. Information concerning the benefits of imaging based on hypoxia is discussed on page 2, line 25 through page 3, line 25. Examples of tumor hypoxia targeting ligands are disclosed on page 5, lines 24-25. Information pertaining to the conjugation chemistry of these ligands is provided on page 6, line 4-19. A discussion pertaining to the assessment of tumor hypoxia by imaging can be found on page 29, line 26 through page 30, line 4. Imaging hypoxia due to stroke using ^{99m}Tc-EC-metronidazole is discussed on page 30, line 22 through page 31, line 15. Example 2 and FIGS. 7-15 disclose information pertaining to the synthesis and stability of ^{99m}Tc-EC-metronidazole, and imaging studies using this agent. Page 45, line 9 through page 53, line 13.

37. The specification also provides substantial guidance pertaining to the preparation of EC-targeting ligand conjugates (see, *e.g.*, page 7, lines 5-13 and page 20, lines 7-15), and the radionuclide labeling of these EC-targeting ligand derivatives (see, *e.g.*, page 7, lines 15-20 and page 7, line 17 through page 22, line 16; page 21, line 6 through page 22, line 16; page 23, line 23 through page 24, line 16). This information can be directly applied in the synthesis of radiolabeled EC-tumor hypoxia targeting ligand conjugates.

38. *Reference Materials Available Around the Priority Date of the Patent Application*

At the time of filing of the patent application, there was substantial information available regarding tumor hypoxia targeting ligands in the context of unrelated inventions. A number of hypoxia-selective antitumor agents had been identified. For example, Hay *et al.* (1994) (Exhibit 52) identified bis(nitroimidazolyl)alkanecarboxamides as a new class of hypoxia-selective antitumor agents using *in vitro* and *in vivo* cytotoxicity and hypoxic cell radiosensitization assays. Garayoa *et al.*, 2000 (Exhibit 53), identified adrenomedullin as a tumor hypoxia marker using hypoxic cell culture techniques, Northern blot analysis, confocal immunohistochemistry, and luciferase reporter assays. Fluorine-18-fluoromisonidazole had been identified as an agent that can bind selectively to hypoxic cells *in vitro* and *in vivo* (Rasey *et al.*, 1989, Exhibit 54); Rasey *et al.*, 1990, Exhibit 55). U.S. Patent 5,688,487 (Exhibit 56) described particular complexes of a metal, a hypoxia-localizing moiety, and a complexing ligand for use in imaging, where in certain embodiments the hypoxia-localizing group is a hypoxia-mediated nitro-heterocyclic group. The phrase "tumor hypoxia targeting ligand" would have been understood to refer to a limited number of specific compounds that can detect the presence of hypoxia in tumors. For many years, scientists have been working with the development and use of [F-18]Fluoromisonidazole in the laboratory setting for the detection and measurement of tumor hypoxia in animals.

39. Regarding the incorporation of bioactive compounds into the radiolabeled agents, Yang *et al.*, 1999b (Exhibit 57), one of the publications of the present inventors, developed a ^{99m}Tc-labeled metronidazole (MN) using EC as a chelator and determined that it was feasible to use this agent to image tumor hypoxia. Thus, use of tumor hypoxia markers

as targeting ligands was well-established, and the level of expertise of those in this field was high.

40. One of ordinary skill in the synthesis and use of radionuclide imaging agents, upon reading the specification, would have been able to make and use the claimed radionuclide-labeled tumor hypoxia targeting ligand conjugates without an undue amount of experimentation. One of ordinary skill in the synthesis and use of radionuclide imaging agents would have understood that a "tumor hypoxia targeting ligand" refers to a member of a specific group of agents that can be readily identified, and that the claims of the invention particularly point out and distinctly claim the subject matter that is the invention. I believe the claimed technology will provide the critical linkage necessary for the development and successful clinical study of new tumor hypoxia targeting agents.

41. Claims Pertaining to Agents that Mimics Glucose

Specification

Aspects of the present invention that include agents that mimic glucose as the tissue-specific ligand are discussed throughout the specification. For instance, examples of agents that mimic glucose are discussed on page 5, line 29 through page 6, line 3. Information pertaining to the conjugation chemistry of these ligands can be found in the specification on page 6, lines 4-19 and page 22, lines 18-28. A discussion regarding tumor glycolysis targeting is found on page 31, lines 20-29. Example 6 and FIGS. 40-48 pertain to tumor glycolysis targeting and the development of ^{99m}Tc-EC-neomycin. Page 60, line 23 through page 64, line 26. In addition, tumor metabolic imaging with ^{99m}Tc-

EC-deoxyglucose is addressed in Example 7 and FIGS. 66-86. Page 65, line 4 through page 68, line 12.

42. Furthermore, the specification provides substantial guidance pertaining to the preparation of EC-targeting ligand conjugates (see, *e.g.*, page 7, lines 5-13 and page 20, lines 7-15), and the radionuclide labeling of these EC-targeting ligand derivatives (see, *e.g.*, page 7, lines 15-20 and page 7, line 17 through page 22, line 16; page 21, line 6 through page 22, line 16; page 23, line 23 through page 24, line 16). This information can be directly applied in the synthesis of radiolabeled conjugates that include agents that mimic glucose.

43. *Reference Materials Around the Priority Date of the Patent Application*

The phrase "an agent that mimics glucose" would have been understood to refer to specific compounds which target glucose metabolism. Around the priority date of the patent application at issue, it was known that the propensity to catabolize glucose at elevated rates was among the most common biochemical characteristics of cancer cells. Reviewed in Fanciulli *et al.*, 1994 (Exhibit 58). This feature of cancer cells led to investigation to identify agents that mimic glucose that could be applied in the diagnosis and treatment of cancer in the context of other inventions. For many years, scientists had been working with compounds such as [14C]deoxyglucose, which are agents that mimic glucose

44. For over three decades, ^{18}F-FDG has been studied by scientists throughout the world and during the past fifteen years, it has grown to be widely used in nuclear medicine in the

context of other inventions. FDG is an agent that mimics glucose. Kanazawa *et al.* (1997) (Exhibit 59) reported on the potential of 2-deoxy-2-[^{18}F] fluoro-D-glucose (FDG), as an NMR pharmaceutical for cancer diagnosis. *In vivo* and *ex vivo* NMR studies were employed in Kanazawa *et al.* to identify FDG as an NMR pharmaceutical for cancer diagnosis. U.S. Patent 4,789,542 (Exhibit 60) described radioiodinated branched carbohydrates for tissue imaging that include a glucose analogue and a vinyl functional group. See abstract and claim 1. Examples of glucose analogues disclosed in the '542 patent include those analogues shown in claims 2 and 3. U.S. Patent 5,643,883 (Exhibit 61) disclosed methods of inhibiting the import of glucose-6-phosphate into the endoplasmic reticulum of a cell, comprising the step of administering a pharmacologically effective dose of a glucose analogue to said cell. Abstract and claim 1. The glucose analogues disclosed in the '883 patent included competitive inhibitors of glucose-6-phosphate uptake, including 2-deoxyglucose-6-phosphate, glucosamine-6-phosphate and N-acetylglucosamine-6-phosphate. Column 5, lines 53-64.

45. Much information was available regarding the structure and function of aminoglycosides, which are agents that mimic glucose (see, *e.g.*, review by Wright *et al.*, 1998, Exhibit 62). U.S. Patent 4,279,992 (Exhibit 63) describes use of aminoglycosides as targeting ligands that can be used to practice the invention directed to a homogeneous specific binding assay method for determining a ligand in a liquid medium. See claims 1 and 11-14. In a study evaluating interactions between RNA and ligands, 3D-SAR analysis was used to study the bound conformations of aminoglycoside ligands with Rev-binding element

RNA (LeClerc and Cedergren, 1998, Exhibit 64). Thus, aminoglycosides were in active use as targeting ligands around the priority date of the application.

46. Therefore, a person of ordinary skill in the synthesis and use of radionuclide imaging agents, upon reading the specification, would have been able to make and use the claimed radionuclide-labeled conjugates incorporating agents that mimic glucose without an undue amount of experimentation. One of ordinary skill in the synthesis and use of radionuclide imaging agents would have understood that an "agent that mimics glucose" refers to a member of a specific group of agents that can be readily identified, and that the claims of the invention particularly point out and distinctly claim the subject matter that is the invention.

47. In conclusion, claims 2-4, 6, 8-10, 15, 23, 30, 31, 33-35, and 37-41 of the above-referenced patent application contain subject matter which was described in the specification of the above-referenced application in such a way as to enable one of ordinary skill in the synthesis and use of radionuclide imaging agents to make and use the invention. The description of the invention provided in the specification is sufficiently clear and concise such that one of ordinary skill in the synthesis and use of radionuclide imaging agents would be able to make the claimed agents and practice the claimed methods without an undue amount of experimentation. The potential number of EC-targeting ligand complexes is not vast and unlimited. Rather, each of the groups set forth by the phrases "anticancer agent," "tumor marker," "folate receptor targeting ligand," "tumor apoptotic cell targeting ligand," "tumor hypoxia targeting ligand," and "an agent that mimics glucose" are limited, and targeting ligands belonging to each of these groups

can be identified using techniques known to those of ordinary skill in the synthesis and use of radionuclide imaging agents. As set forth above, the art pertaining to the synthesis and use of EC-targeting ligand complexes was highly advanced at the time of filing of the application, and determining which types of targeting ligand complexes would bind EC and generate results would not have required an undue amount of experimentation. As a result, there would be predictability in practicing the claimed invention. Furthermore, the working examples presented in the specification are sufficient to enable the public to prepare the claimed radionuclide labeled complexes.

48. In addition, based on my review of the specification and in view of the above-cited literature pertaining to the phrases "anticancer agent," "tumor marker," "folate receptor targeting ligand," "tumor apoptotic cell targeting ligand," "tumor hypoxia targeting ligand," and "an agent that mimics glucose," the present claims particularly point out and distinctly claim the subject matter that the inventors believe is the invention. In particular, the phrases "anticancer agent," "tumor marker," "folate receptor targeting ligand," "tumor apoptotic cell targeting ligand," "tumor hypoxia targeting ligand," and "an agent that mimics glucose" are not confusing, nor are they unlimited in their scope. The phrases referenced above are not unlimited in scope and someone skilled in the art would not and should not be confused by what such phrases mean. Rather, these phrases are definite because they refer to specific classes of targeting ligands whose members can be identified using techniques well-known to those who have an ordinary understanding of the synthesis and use of radionuclide imaging agents.

49. I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

12/22/2004

Date

Jerry L. Bryant, Jr., M.S.

APPENDIX A

Revised: 12/16/04

CURRICULUM VITAE

NAME: Jerry L. Bryant, M.S.

TITLE/AFFILIATION:

(a) Primary Appointment:
Chief Technology Officer — Present
Head of Sciencitifc Evaluation
Division of Business Development
Cell>Point, LLC

(b) Joint/Adjunct Appointment:
Research Assistant II — Oct. 2002-June, 2003
Department of Experimental Nuclear Medicine
Division of Diagnostic Imaging
University of Texas M.D. Anderson Cancer Center
Houston, TX

Director of Research and Development — Present
Verimed Research Corporation
Houston, TX 77098

BIRTHDATE/PLACE: August 27, 1966, Louisiana

CITIZENSHIP: U.S. Citizen

HOME ADDRESS: 6861 Staffordshire Blvd.
Houston, Texas 77030
TELEPHONE: 713-797-6689

OFFICE ADDRESS: Cell>Point,LLC
Division of Business Dev
7120 East Orchard Rd., Suite 350
Englewood, CO 80111
e-mail: cellpoint@swbell.net
TELEPHONE: 303-689-9693
FAX: 303-689-0198

MARITAL STATUS: Married

LICENSURES-ACTIVE: None

EDUCATION:

GRADUATE: University of Florida, M.S.
Microbiology & Cell Science w/Molecular Biology,
January, 1990-December, 1991, Gainesville, FL

UNDERGRADUATE: Tennessee State University, B.S.
Chemistry w/Biochemistry
June, 1984-May, 1987, Nashville, Tennessee

POSTGRADUATE TRAINING:
None

SPECIALITY BOARDS: None

MILITARY/GOVERNMENT: None

ACADEMIC & PROFESSIONAL APPOINTMENTS:

Chief Technology Officer
Division of Business Development
Cell>Point, LLC
(2001-present)

Research Assistant
Department of Experimental Nuclear Medicine
Division of Diagnostic Imaging
University of Texas M. D. Anderson Cancer Center,
(2002-2003)

Director of Research and Development
Division of Business Development,
Verimed Research Corporation
Houston, TX
(2002-2004)

Chief Scientific Officer
Division of Business Development
Allcure, Inc.
Houston, TX
(May, 2001-May, 2002)

President/Board Director
Allcure JEMA Medicine Services, Inc.
Medical and Research Supply Distributor
Houston, TX
(January, 1996-April, 2001)

Research Assistant II
Department of Medicine
Division of Pathology
Molecular Pathology
The University of Texas M.D. Anderson Cancer Center
Houston, TX
(November, 1994-March, 1999)

Volunteer Technician
Department of Anesthesiology
University of Florida
Gainesville, FL
(July, 1994-September, 1994)

Research Assistant
Department of Anesthesiology
University of Florida
Gainesville, FL
(August, 1992-June, 1994)

Research Associate
Department of Medicine
Division of Cardiology
Cardiovascular Disease
VA Medical Center
University of Florida
Gainesville, FL
(November, 1993-February, 1994)

Research Associate
Department of Medicine
Division of Cardiology
Cardiovascular Disease
University of Florida
Gainesville, FL
(October, 1991-March, 1992)

Research Technician
Department of Pediatric Hematology and Oncology
University of Florida
Gainesville, FL
(October, 1991-March, 1992)

Teaching Assistant
Department of Microbiology and Cell Science
University of Florida
Gainesville, FL
(January, 1991-May, 1991)

Research Assistant
Department of Microbiology and Cell Science/Molecular Biology
University of Florida
Gainesville, FL
(August, 1989-August, 1991)

Graduate Student
Department of Microbiology and Cell Science/Molecular Biology
University of Flordia
Gainesville, FL
(August, 1989-August, 1991)

Summer Miniorty Graduate Program
University of Florida
Gainesville, FL
(June, 1989-August, 1989)

a) Consultantships

Board of Director Member
Cell>Point, LLC
Englewood, CO
(May, 2001-Present)

Advisory Scientific Board Member
Cell>Point, LLC
Englewood, CO
(March, 2003-Present)

Board of Director Member
Verimed Research Corporation
Houston, TX
(August, 2002-Present)

ADMINISTRATIVE APPOINTMENTS AND RESPONSIBILITIES:

Director of Clinical Trial Research Protocol
Sponsor by Cell>Point, LLC
Department of Nuclear Medicine & Radiation Oncology
Division of Diagnostic Imaging
(June, 2002-present)

Director of a Pilot Biodistribution and Pharmacokinetics Study of 99mTc-EC-Annexin V in patients with Breast Cancer
Sponsor by Cell>Point, LLC
Department of Breast Medical Oncology & Division of Diagnostic Imaging
(April, 2003-May, 2004)

Director of a Pilot Imaging study of COX-2 expression with 99mTc-Celecoxib Spectro-Computer Tomography in Colorectal Cancer
Sponsor by Cell>Point, LLC
Department of Gastrointestinal Medical Oncology & Division of Diagnostic Imaging
(April, 2003-present)

COMMITTEE MEMBERSHIPS:

a) M.D. Anderson Committee Memberships/Chairmanships:

Member of the Core Logistics Committee for Clincial Trial Project
The University of Texas MD Anderson Cancer Center
(March, 2003-present)

b) Society Memberships with Offices held:

Member, American Association for Cancer Research,
(January, 2003-Present)

Member, M. D. Anderson Associates,
(October, 2002-Present)

Member, Society of Nuclear Medicine,
(June, 2002-Present)

Member, American Association for the Advancement of Science,
(August, 2001-Present)

Member, American Association of Microbiology,
(January, 1990-Present)

Member, American Chemical Society,
(June, 2002-Present)

EDITORSHIPS AND EDITORIAL BOARD MEMBERSHIPS:

Journal Reviewer:

None

HONORS AND AWARDS:

None

LECTURESHIPS AND VISITING PROFESSORSHIPS:

The 42nd American College of Cardiology Annual Scientific Session
Anaheim, CA
(March, 14-18, 1993)

ORGANIZATION OF NATIONAL OR INTERNATIONAL CONFERENCES

International:

None

PATENTS PENDING AND GRANTED:

1. Yang, D.J., Yu, D-F, Oh, C-S, and **Bryant, J.**: Ethylenedicysteine (EC)-Drug Conjugates Compositions and Methods for Tissue Specific Disease Imaging , US patent S/N 10/703,405. UTMDACC:02-073 (UTXC:758USP1), 11/7/2003 filed, US Patent (pending).

2. Yang, D.J., Oh, C-S, Kohanim, S., Yu, D-F, Azhdarinia, A. and **Bryant, J.**: Mechanism-based Targeted Pancreatic Beta Cell Imaging and Therapy, US patent S/N. UTMDACC/VeriMed Research Corporation: (10/942,615 and IPA# PCT/US04/30374), 9/10/03 filed, US patent (pending).

3. Yang, D.J., Yu, D-F, Oh, C-S, and **Bryant, J.**: N2S2 Chelate-Targeting Ligand Conjugates, US patent S/N 10/732,919. UTSC:841US-MDA02-073, 12/10/2003 filed, US patent (pending).

GRANT/CONTRACT SUPPORT: (last 5 years)

CT and MRI functional agents develpoment and evaluation (SR 2002-00007147SM). Director: **Bryant, J.L.** P.I. Yang, D.J. Supported by VeriMed Research Corporation (Houston, TX). August, 2002-August 1, 2007, $1,000,000 ($200,000/year).

^{99m}Tc-Ethylenedicysteine (EC)-Drug Conjugates for Tissue Specific Disease Imaging (LS01-212), Director: **Bryant, J.L.** P.I. Yang, D.J. Supported by Cell> Point , LLC (Englewood, CO). June 15, 2001-June 15, 2006, $1,000,000 ($200,000/year).

"Human Malignant Lymphoma Models in Immune Deficient Mice" (LS01-123), Director: **Bryant, J.L.**, P.I. Ford, RJ. Supported by VeriMed Research Corporation (Houston,TX). July, 2001-July, 2006, $1,280,000 ($256,000/year).

Assessment of Tumor Factors with 99mTc-EC-Deoxglucose for effective imaging Guided Therapy and by utilizing the EC-Technology for Targeting Specific Regulatory Functions (-01), P.I.: **Bryant, J.L.**, NIH-NCI (R21/R33) June 21, 2003-Spetember 30, 2006, $1,572,249 (Submitting).

Director "**Bryant, J.L**"., of Clinical Trial Research Protocol " Comparison of Tc-99m-EC-Deoxyglucose (EC-DG) and FDG-PET Scans for 1) the Evaluation of Patients Suspected of Having Persistent/Recurrent Squamous Cell Carcinoma of the Larynx after Definitive Treatment with Radiation Therapy and 2) the Evaluation of Primary Lung Cancer Patients", Sponsor by Cell>Point, LLC, March 10, 2003- March 10, 2005, Funding $560,000 for two years.

Director **"Bryant, J.L."** of a Pilot Biodistribution and Pharmacokinetics Study of "99mTc-EC-Annexin V in patients with Breast Cancer", Sponsor by Cell>Point, LLC, Activated May 1, 2003-May 1, 2004, Funding $25,000 for one year.

Director **"Bryant, J.L."** of a Pilot Imaging study of COX-2 expression with "99mTc-Celecoxib Spectro-Computer Tomography in Colorectal Cancer", Sponsor by Cell>Point, LLC, Activated June 1, 2003-June 1, 2004, Funding $25,000 for one year.

TEACHING EXPERIENCES:

Courses Taught:

Microbiology Laboratory, University of Florida, Nursing Students
January, 1991-May, 1991.

Training Programs: None

Other Educational Programs: None

SUPERVISORY TEACHING
Advisory Committees: None

Supervisory committees: None

Students/Postgraduates directly supervised: None

Clinical Fellows: None

Medical/Undergraduate Students: None

INVITATIONS TO NATIONAL OR INTERNATIONAL CONFERENCES: None

BIBLIOGRAPHY

PUBLISHED ARTICLES IN REFERRED JOURNALS

1. 1. **Bryant JL Jr.**, Mehta P, Von der Porten A, Mehta, JL: Co-Purification of 130 kD nitric oxide synthase and a 22 kD link protein from human neutrophils. Biochemical and Biophysical Research Communications 189: 558-564, 1992.

2. Mehta JL, **Bryant JL Jr.**, Mehta P: Reduction of Nitric oxide synthase activity in human neutrophils by oxidized low-density lipoproteins. Biochemical Pharmacology, Vol.50,No. 8,pp. 1181-1195, 1995.

3. Yang BC, **Bryant JL Jr.**, Saldeen TGP, Mehta JL: Dietary fish oil protects against ischemia-reperfusion induced myocardial dysfunction and alters vascular response without affecting nitric oxide synthesis in rats. American Heart Journal, 1993.

4. Mehta JL, Lopez LM, **Bryant JL**, Cox G: Salutary effect of antihypertensive therapy with celiprolol on nitric oxide synthase activity, superoxide anion generation and platelet aggregation in hypertensive subjects. Circulation, 1993.

5. B.C. Yang, T.G.P. Saldeen, **J.L. Bryant**, W.W. Nichols and J.L. Mehta: Long-term dietary fish oil supplementation protects against ischemia-reperfusion-induced myocardial dysfunction in isolated rat hearts. American Heart Journal, 126: 1287-92, 1993.

6. **Bryant, J.**, Pham, L., Yoshimura, L., Tamayo, A., Ordonez, N. and Ford, RJ. Development of intermediate-grade (mantle cell) and low-grade (small lymphocytic and marginal zone) human non-Hodgkin's lymphomas xenotransplanted in severe combined immunodeficiency mouse models. Laboratory Investigation, 80:557-573, 2000.

7. Yang, D.J., Kim, K-D, Schechter, N.R., Yu, D-F, Wu, P., Azhdarinia, A., Roach, J.S., Kohanim, S., Ozaki, K., Fogler, W.E., **Bryant, J.L.**, Herbst R.S., Abbruzzes J., Kim, E.E., and Podoloff, D.A. Assessment of Antiangiogenic Effect Using ^{99m}Tc-EC-Endostatin. Cancer Biotherapy and Radiopharmaceuticals. 17(2): 233-246, 2002.

8. Schechter, N.R., Yang, D.J., Azhdarinia, A., Kohanim, S., Wendt, R., Oh, C-S, Hu, M., Yu, D-F, **Bryant, J.**, Ang, K.K., Forster, K.M., Kim, E.E., and Podoloff, D.A. Assessment of EGF receptors with ^{99m}Tc-ethylenedicysteine-C225 monoclonal antibody. Anti-Cancer Drugs, 14: 49-56, 2003.

9. Yang, D.J., Kim, C-G, Schechter, N.R., Azhdarinia, A., Yu, D-F, Oh, C-S, **Bryant, J.L.**, Won, J.J., Kim, E. E., Podoloff, D.A. Imaging with ^{99m}Tc-EC-DG Targeted at the Multifunctional Glucose Transport System: Feasibility study with rodents. Radiology, 226: 465-473, 2003.

10. Yang DJ, Bryant J, Chang JY, Mendez R, Oh C-S, Yu D-F, Ito M, Azhdarinia A, Kohanim S, Kim EE, Lin E, Podoloff DA. Assessment of COX-2 expression with ^{99m}Tc-labeled celebrex. Anti-Cancer Drugs 15:255-263, 2004.

11. Yang DJ, Yukihiro M, Oh C-S, Kohanim S, Azhdarinia A, Yu D-F, Kim C-G, Ito M, Bryant JL, Kim EE, Podoloff DA. Assessment of Therapeutic Tumor Response Using ^{99m}Tc-Ethylenedicysteine-Glucosamine. Cancer Biotherapy and Radiopharm. 19(4):444-458, 2004.

12. Yang DJ, Ozaki K, Oh C-S, Azhdarinia A, Ito M, Greenwell AC, Bryant JL, Kohanim S, Kim EE. ^{99m}Tc-EC-Guanine: assessment of tuomor growth using ^{99m}Tc-EC-guanine. Chemotherapy 2004 (submitted).

13. Yang DJ, Oh C-S, Kohanim S, Ito M, Bryant JL, Yu D-F, Azhdarinia A, Greenwell AC, Kim JH, Kim EE. Imaging pancreas beta-cell sulfonylurea receptors with ^{99m}Tc-DTPA-sulfonylurea receptor agents. Diabetes 2004 (submitted).

Articles Submitted:

1. **Bryant JL Jr.**, Von der Porten A, Nicolini FA, Mehta P, Mehta JL: Oxidized low density lipoprotein decrease superoxide radical generation and increase platelet-inhibitory activity in human neutrophils.

2. Mehta P, **Bryant JL Jr.**, Mehta JL: The effect of oxidized low density lipoproteins on nitric oxide synthase in human neutrophils.

3. **Bryant JL Jr.**, Mehta P, Mehta JL: Identification of calcium-dependent nitric oxide synthase in human neutrophil membrane.

Published Abstracts:

1. **Bryant JL Jr.**, Yang BC, Mehta P, Saldeen TGP, Mehta JL: Dietary fish oil decreases superoxide radical generation without affecting nitric oxide synthase activity: a mechanism of vasorelaxation. Journal of the American College of Cardiology 21 430A, 1993.

2. Lopez LM, **Bryant JL Jr.**, Mehta JL: Effect of combined beta and alpha-adrenergic blockade on nitric oxide sythntase activity, superoxide generation and platelet aggregation in patients with hypertension. Proceeding of the American College of Clinical Pharmacology, 1993.

3. Lopez LM, **Bryant JL Jr.**, Mehta JL: Effects of therapy with celiprolol on nitric oxide synthase activity, superoxide generation and platelet aggregation in patients with hypertension. Journal of the American College of Cardiology, 1994.

4. Ford, RJ., **Bryant, J.**, Claypool, K. and Cabanillas, F: Human lymphoma models in SCID mice: Non-Hodgkin and Hodgkin's. Blood, 87, 1996.

5. Ford, RJ., Luthra R., **Bryant,J.**, Tamayo, A., Curiel,T: In vitro and in vivo models for mantle cell lymphoma. Blood, 92:314a, 1998.

6. A. Azhdarinia, D.J. Yang, S., Zakko, M., Yukihiro, D-F Yu, **J.L. Bryant**, S. Kohanim, E.E. Kim, D.A., Podoloff. Targeted tumor imaging using ^{99}mTc-EC-deoxyglucose in comparison with ^{18}F-FDG. Presented at the 49th Annual Meeting of the Society of Nuclear Medicine, Los Angeles, CA, June 15-19, 2002.

6. A. Azhdarinia, M. Yukihiro, D.J. Yang, **J.L. Bryant**, C-G Kim, D-F Yu, S. Kohanim, E.E. Kim, D.A. Podoloff. Imaging angiogenesis using ^{99}mTc-EC-endostatin. Presented at the 49th Annual Meeting of the Society of Nuclear Medicine, Los Angeles, CA, June 15-19, 2002.

7. N.R. Schechter, D.J. Yang, K. Ang, D-F Yu, L.W. Tansey, **J.L. Bryant**, E.E. Kim, D.A. Podoloff. Preliminary Tumor EGF Receptor imaging with ^{99}mTc-EC-C225. Presented at the 49th Annual Meeting of the Society of Nuclear Medicine, Los Angeles, CA, June 15-19, 2002.

8. D.J. Yang, H.A. Macapinlac, D-F. Yu, A. Azhdarinia, S. Kihanim, **J.L. Bryant**, E.E. Kim, D.A. Podoloff. Glucosamine pathway imaging using ^{99}mTc-EC-deoxyglucose in comparison with ^{18}F-FDG. Presented at the 49th Annual Meeting of the Society of Nuclear Medicine, Los Angeles, CA, June 15-19, 2002.

9. C-S Oh, D.J. Yang, C-G Kim, D-F Yu, M. Yukihiro, S. Kohanim, A. Azhdarinia, **J.L. Bryant**, E.E. Kim, D.A. Podoloff. ^{99}mTc-labeled nitroimidazole analogues for assessment of tumor hypoxia. Presented at the 49th Annual Meeting of the Society of Nuclear Medicine, Los Angeles, CA, June 15-19, 2002.

10. M. Yukihiro, D.J. Yang, T. Inoue, D-F Yu, S. Kohanim, A. Azhdarinia, **J.L. Bryant**, E.E. Kim, D.A. Podoloff. In vitro cellular uptake and in vivo biodistribution of ^{99}mTc-EC-Angiostatin. Presented at the 49th Annual Meeting of the Society of Nuclear Medicine, Los Angeles, CA, June 15-19, 2002.

11. Schechter, N. R., Yang, D. J., Ang, K., Yu, D-F, Tansey, L.W., **Bryant, J. L.**, Kim, E. E. , Podoloff, D. A. Preliminary tumor egf receptor imaging with ^{99m}Tc-EC-C225. Presented at the 49th Annual Meeting of the Society of Nuclear Medicine, Los angeles, CA June 15-19, 2002. J. Nucl. Med. 43 (5): 269, 2002 (Abstract 1088).

12. Azhdarinia, A., Yang, D. J., Zakko, S., Yukihiro, M., Yu, D-F, **Bryant, J. L.**, Kohanim, S., Kim, E. E. , Podoloff, D. A. Targeted tumor imaging using ^{99m}Tc-EC-deoxyglucose in comparison with ^{18}F-FDG. Presented at the 49th Annual Meeting of the Society of Nuclear Medicine, Los angeles, CA June 15-19, 2002. J. Nucl. Med. 43 (5): 273, 2002 (Abstract 1102).

13. Azhdarinia, A., Yukihiro, M., Yang, D. J., **Bryant, J. L.**, Kim, C-G, Yu, D-F, Kohanim, S., Kim, E. E. , Podoloff, D. A. Imaging angiogenesis using ^{99m}Tc-EC-endostatin. Presented at the 49th Annual Meeting of the Society of Nuclear Medicine, Los angeles, CA June 15-19, 2002. J. Nucl. Med. 43 (5): 121, 2002 (Abstract 435).

14. Yang, D. J., Macapinlac, H.A., Yu, D-F, Azhdarinia, A., Kohanim, S., **Bryant, J. L.**, Kim, E. E. , Podoloff, D. A. Glucosamine pathway imaging using ^{99m}Tc-EC-deoxyglucose in comparison with ^{18}F-FDG. Presented at the 49th Annual Meeting of the Society of Nuclear Medicine, Los angeles, CA June 15-19, 2002. J. Nucl. Med. 43 (5): 368, 2002 (Abstract 1478).

15. Azhdarinia, A., Yang, D. J., Schechter, N. R., Yu, D-F, **Bryant, J.**, Kohanim, S., Kim, E.E., Podoloff, D.A. ^{99m}Tc-EC-C225: An EGFR Targeting Tracer To Assess Angiogenesis. Presented at the 6th International Symposium on Technetium, Rhenium and other Metals in Chemistry and Nuclear Medicine,, Bressanone, Italy, September 4-7, 2002 (Abstract # CP5).

16. Azhdarinia, A., Yang, D. J., Yukihiro, M., Yu, D-F, **Bryant, J.**, Kim, E.E., Podoloff, D.A. ^{99m}Tc- Labeled Endostatin and Angiostatin for Angiogenesis Imaging. Presented at the 6th International Symposium on Technetium, Rhenium and other Metals in Chemistry and Nuclear Medicine, Bressanone, Italy, September 4-7, 2002 (Abstract # BP1).

17. **Jerry Bryant**, David J. Yang, Ali Azhdarinia, Edward Lin, Edmund E. Kim, Donald A. Podoloff. Radiosynthesis, Biodistribution and Planar Scintigraphy of

99mTc-Labeled Celebrex in DMBA-induced tumor bearing rats: Presented at the 94th American Association for Cancer Research 2003 Annual Meeting, Toronto, Canada, April 5-9. (Abstract # 107933).

18. M. Yukihiro, D.J. Yang, A. Azhdarinia, D-F Yu, C-G Kim, S. Kohanim, **J.L. Bryant**, E.E. Kim, D.A. Podoloff. Assessment of Tumor Growth with 99mTc-EC-Glucosamine: Presented at the 50th Annual Meeting of the Society of Nuclear Medicine, New Orleans, Louisiana, June 21-25, 2003. J. Nucl. Med. 43 (5): 368, 2002 (Abstract 1478).

19. A. Azhdarinia, D. J. Yang, M. Yukihiro, **J. L. Bryant**, D-F Yu, S. Kohanim, E. E. Kim, D. A. Podoloff. Imaging, Dosimetry and Acute Toxicity with 99mTc-EC-Deoxyglucose in Tumor-Bearing Animals. Presented at the 50th Annual Meeting of the Society of Nuclear Medicine, New Orleans, Louisiana, June 21-25, 2003. J. Nucl. Med. 43 (5): 368, 2002 (Abstract 1478).

20. A. Azhdarinia, D. J. Yang, M. Yukihiro, C. K. S. Chao, D-F Yu, **J. L. Bryant**, E. E. Kim, D. A. Podoloff. 99mTc-Labled Endostatin and Angiostatin for Angiogenesis Imaging. Presented at the 50th Annual Meeting of the Society of Nuclear Medicine, New Orleans, Louisiana, June 21-25, 2003. J. Nucl. Med. 43 (5): 368, 2002 (Abstract 1478).

21. R. Mendez, C-S Oh, A. Azhdarinia, D. J. Yang, D-F Yu, M. Yukihiro, **J. L. Bryant**, E. E. Kim, D. A. Podoloff. In-Vitro and In-Vivo evalutation of 99mTc-EC-Doxorubicin as a marker of Mdr to Doxorubicin. Presented at the 50th Annual Meeting of the Society of Nuclear Medicine, New Orleans, Louisiana, June 21-25, 2003. J. Nucl. Med. 43 (5): 368, 2002 (Abstract 1478).

22. C-S Oh, D. J. Yang, M. Yukihiro, A. Azhdarinia, D-F Yu, C-G Kim, S. Kohanim, **J. L. Bryant,** E. E. Kim, D. A. Podoloff. Synthesis and evaluation of adenosine analogue in tumor-bearing rodents for assessment of tumor cell proliferation. Presented at the 50th Annual Meeting of the Society of Nuclear Medicine, New Orleans, Louisiana, June 21-25, 2003. J. Nucl. Med. 43 (5): 368, 2002 (Abstract 1478).

23. S. Kohanim, C. Sharma, M. Yukihiro, D. J. Yang, A. Azhdarinia, D-F Yu, **J. L. Bryant**, E. E. Kim, D. A. Podoloff. Targeting Lipid metabolism with 99mTc-EC-TML: A carnitine Analogue. Presented at the 50th Annual Meeting of the Society of Nuclear Medicine, New Orleans, Louisiana, June 21-25, 2003. J. Nucl. Med. 43 (5): 368, 2002 (Abstract 1478).

24. D. J. Yang, A. Azhdarinia, M. Yukihiro, D-F Yu, C-S Oh, **J. L. Bryant**, S. Zakko, E. E. Kim, D. A. Podoloff. Assessment of tumor growth using angiogenic and apoptotic agents. Presented at the 50th Annual Meeting of the Society of Nuclear Medicine, New Orleans, Louisiana, June 21-25, 2003. J. Nucl. Med. 43 (5): 368, 2002 (Abstract 1478).

25. A. Azhdarinia, D. J. Yang, **J. L. Bryant**, M. Yukihiro, D-F Yu, C-S Oh, S. Kohanim, E. E. Kim, D. A. Podoloff. Radiosynthesis, Biodistribution and Planar Scintigraphy of

99mTc-EC-Coxi in tumor bearing animal models. Presented at the 50th Annual Meeting of the Society of Nuclear Medicine, New Orleans, Louisiana, June 21-25, 2003. J. Nucl. Med. 43 (5): 368, 2002 (Abstract 1478).

26. A. Azhdarinia, D.J. Yang, D-F Yu, C. Chao, E. Lin, J. Bryant, E.E. Kim, D.A. Podoloff. 99mTc-EC-COXi: Biodistribution and planar scintigraphy in mammary tumor-bearing animal models. Presented at the 2003 Annual Meeting of American Society of Clinical Oncology, Chicago, Illinois, May 31-June 3, 2003.

27. Yukihiro M, Yang DJ, Azhdarinia A, Yu D-F, Kim C-G, Kohanim S, Bryant JL, Kim EE, Podoloff DA. Assessment of tumor growth with ^{99m}Tc-EC-glucosamine. J Nucl Med 44 (5):299, 2003 (Abstract 1071).

28. Azhdarinia A, Yang DJ, Yukihiro M, Chao CKS, Yu D-F, Bryant JL, Kim EE, Podoloff DA. ^{99m}Tc-labled endostatin and angiostatin for angiogenesis imaging. J Nucl Med 44 (5): 302, 2003 (Abstract 1082).

29. Azhdarinia A, Yang DJ, Yukihiro M, Bryant JL, Yu D-F, Kohanim S, Kim EE, Podoloff DA. Imaging, dosimetry and acute toxicity with ^{99m}Tc-EC-deoxyglucose in tumor-bearing animals. J Nucl Med 44 (5):323, 2003 (Abstract 1158).

30. Kohanim S, Sharma C, Yukihiro M, Yang DJ, Azhdarinia A, Yu D-F, Bryant JL, Kim EE, Podoloff DA. Targeting lipid metabolism with ^{99m}Tc-EC-TML: a carnitine analogue. J Nucl Med 44 (5):301, 2003 (Abstract 1077).

31. Oh C-S, Yang DJ, Yukihiro M, Azhdarinia A, Yu D-F, Kim C-G, Kohanim S, Bryant JL, Kim EE, Podoloff DA. Synthesis and evaluation of adenosine analogue in tumor-bearing rodents for assessment of tumor cell proliferation. J Nucl Med 44 (5):301, 2003 (Abstract 1078).

32. Mendez R, Oh C-S, Azhdarinia A, Yang DJ, Yu D-F, Yukihiro M, Bryant JL, Kim EE, Podoloff DA. *In vitro* and *in vivo* evaluation of ^{99m}Tc-EC-doxorubicin as a marker of MDR to doxorubicin. J Nucl Med 44 (5): 303, 2003 (Abstract 1084).

33. Ito M, Yang DJ, Azhdarinia A, Mendez R, Kohanim S, Oh C-S, Yu D-F, Bryant JL, Chao CKS, Kim EE. PET and planar imaging of tumor hypoxia with radiolabeled metronidazole. . Proceedings of the AACR 45:104, *2004* (Abstract 946).

34. Mendez R, Bryant J, Yang DJ, Lin E, Chang JY, Ito M, Azhdarinia A, Kim EE, Podoloff DA. Imaging COX-2 expression with ^{99m}Tc-labeled celebrex. Proceedings of the AACR 45:104, *2004* (Abstract 948).

35. Rollo FD, Bryant JL, Yang DJ, Bai C, Kim EE, Yu DF, Ye J, Durbin MK, Garrard DJ, Shao L. The Complementrary Role of FDG and Tc-99m ECDG for Tumor Imaging. Proeedings of the Society of Nuclear Medicine 51st Annual Meeting, June, 2004. (Abstract No. 1062)

36. Azhdarinia A, Yang DJ, Yu DF, Oh C, Kohanim S, Mendez R, Ito M, Bryant JL, Kim EE, Podoloff DA. Local Regional Chemotherapy and Radiotherapy using an *In Situ* Hydrogei and Planar Imaging for Assessment of Tumor Growth. Proeedings of

the Society of Nuclear Medicine 51st Annual Meeting, June, 2004. (Abstract No. 1222)

37. Yang DJ, Chang JY, Mendez R, Bryant J, Azhdarina A, Oh C, Kohanim S, Ito M, Kim EE, Lin E, Podoloff DA. ^{99m}Tc-Labeled Celebrex: Synthesis, In Vitro and In Vivo Assessment of Cox-2 Expression. Proeedings of the Society of Nuclear Medicine 51st Annual Meeting, June, 2004. (Abstract No. 1406)

38. Oh C, Ozaki K, Yang DJ, Zakko S, Inoue T, Azhdarinia A, Bryant JL, Kim CG, Kohanim S, Kim EE, Podoloff DA. Assessment of Tumor Cell Proliferation with 99mTc-Labeled Adenosine and Guanine Analogues. Proeedings of the Society of Nuclear Medicine 51st Annual Meeting, June, 2004. (Abstract No. 1407)

39. Yang DJ, Oh C, Yu DF, Kohanim Azhdarinia A, Ito M, Mendez R, Chanda M. Bryant JL, Kim EE, Podoloff DA. Imaging Sulfonylurea Receptors on the Pancreas Beta-cell using Tc-99m Labeled Sulfonylurea Agents. Proeedings of the Society of Nuclear Medicine 51st Annual Meeting, June, 2004. (Abstract No. 1435)

40. Bai, C, Shao, J, Durbin, MK, Da Silva, AJ, Rollo FD, Garrard DJ, Forster, KM and Bryant, J. SPECT/CT Imaging with three-dimensional detector response correction and CT-based attenuation correction to improve SPECT Oncology. Proeedings of the Society of Nuclear Medicine 51st Annual Meeting, June, 2004. (Abstract No. 10..)

INVITED ARTICLES IN JOURNALS: None

BOOKS AND CHAPTERS:

BOOKS EDITED AND WRITTEN:

BOOK CHAPTERS:

1. Azhdarinia, A., Yang, D. J., Schechter, N. R., Yu, D-F, **Bryant, J.**, Kohanim, S., Kim, E.E., Podoloff, D.A. ^{99m}Tc-EC-C225: An EGFR Targeting Tracer To Assess Angiogenesis. *In*: M. Nicolini and U. Mazzi (eds), Technetium, Rhenium and other Metals in Chemistry and Nuclear Medicine, pp. 665-667, Padova, Italy, Servizi Grafici Editoriali snc, 2002.

2. Azhdarinia, A., Yang, D. J., Yukihiro, M., Yu, D-F, **Bryant, J.**, Kim, E.E., Podoloff, D.A. 99mTc- Labeled Endostatin and Angiostatin for Angiogenesis Imaging. *In*: M. Nicolini and U. Mazzi (eds), Technetium, Rhenium and other Metals in Chemistry and Nuclear Medicine, pp. 387-389, Padova, Italy, Servizi Grafici Editoriali snc, 2002.

REFERENCES

Richard J. Ford, M.D., Ph.D.
Professor of Hematopathology
UT MD Anderson Cancer Center
1515 Holcombe Blvd., Box 72
Houston, TX 77030 Tel. 713/792-3121

David J. Yang, Ph.D.
Associate Professor and Associate Chemist of Nuclear Medicine
Department of Nuclear Medicine
UT MD Anderson Cancer Center
1515 Holcombe Blvd., Box 59
Houston, TX 77030 Tel. 713/794-1053

E. Edmund Kim, M.D.
Professor of Radiology & Medicine
Division of Nuclear Medicine
UT MD Anderson Cancer Center
1515 Holcombe Blvd., Box 59
Houston, TX 77030 Tel. 713/794-1052

F.David Rollo, M.D., Ph.D
Chief Medical Officer
Philips Medical Systems
540 Alder Drive
Milpitas, CA 95035 Tel. 408/468-3634